HETEROCYCLES, Vol. 91, No. 7, 2015, pp. 1423 - 1428. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 15th April, 2015, Accepted, 20th May, 2015, Published online, 29th May, 2015
DOI: 10.3987/COM-15-13228

Cu-MEDIATED OXIDATIVE DIMERIZATION OF SKATOLE TO TRYPTANTHRIN, AN INDOLO[2,1-*b*]QUINAZOLONE ALKALOID

Tomoki Itoh, Takumi Abe, Shuhei Nakamura, and Minoru Ishikura*

School of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan; E-mail: ishikura@hoku-iryo-u.ac.jp

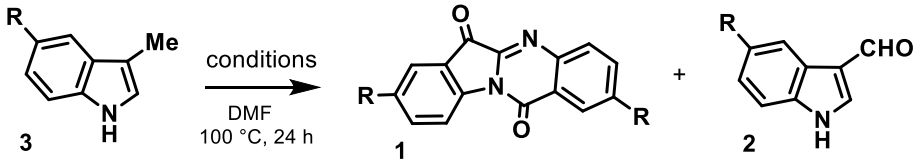
Abstract – A one-pot conversion of skatole to tryptanthrin, an indolo[2,1-*b*]quinazoline alkaloid, was achieved by Cu-mediated oxidation.

Tryptanthrin (**1a**) is an indole alkaloid that was first isolated from a culture of the fungus *Candida lipolytica*.[1] This compound contains an intriguing indolo[2,1-*b*]quinazoline moiety and has potent biological activities,[2] including strong inhibition of pathogenic microorganisms, antifungal activity, antiparasitic activity, and antitumor activity. Therefore, several synthetic methods for **1a** have been reported,[3] typically involving the condensation of isatin with isatoic acid[4] and the reaction of anthranilic acid with isatin in the presence of $SOCl_2$.[5] However, oxidative dimerization of indole-3-carbaldehyde (**2a**) provides a straightforward approach to **1a**. The one-pot formation of **1a** based on the oxone-induced oxidative dimerization of **2a** was achieved by Grundt.[6] We reported the Dakin oxidation of **2a** with urea hydrogen peroxide as an oxidant, where **1a** was obtained through the condensation of **2a** with isatoic anhydride generated in situ from **2a** and further oxidation/cyclization sequences.[7] Recently, a facile formation of 1-methyl-3-indolecarbaldehyde by Cu-catalyzed oxidation of 1-methylskatole and 1-methylgramine using $CuBr_2 \cdot SMe_2$ and DABCO in DMF under O_2 (1 atm) was reported.[8] Therefore, we were interested in investigating the feasibility of a one-pot conversion of skatole (**3a**) and gramine (**4a**) to **1a** involving the intermediate formation of aldehyde **2a** via the oxidation of **3a** and **4a**. Herein, we report one-pot access to **1a** based on Cu-mediated oxidation of **3a** and **4a**.

Initially, **3a** was subjected to aerobic oxidation with $CuBr_2 \cdot SMe_2$ (0.2 equiv) and DABCO (1 equiv) in DMF at 100 °C for 24 h (Table 1). This allowed the isolation of **1a** in 15% yield accompanied by **2a** in 40% yield (Entry 1). However, replacing $CuBr_2 \cdot SMe_2$ with $Cu(OTf)_2$ produced **2a** in 72% yield, and the formation of **1a** was not observed (Entry 2). Using $CuBr_2 \cdot SMe_2$, $Cu(OAc)_2$, and CuBr with PCC as an oxidant did not improve the yield (Entries 3–5). In contrast, using CuI with PCC afforded **1a** in 30% yield without the formation of **2a**. Increasing the catalyst loading to 0.5 equiv provided **1a** in 37% yield (Entries 6 and 7). Moreover, the reaction was accelerated by increasing the amounts of PCC (2 equiv) and

CuI (1.1 equiv), which produced **1a** in 52% yield (Entry 9). Oxidation of **3a** with PCC resulted in the formation of **2a** in 20% yield (Entry 10). In addition, treating 5-substituted skatoles **3b**, **3c**, and **3d** under the identified conditions provided **1b**, **1c**, and **1d** in 33%, 30%, and 27% yields, respectively (Entries 11–13). The formation of **1** from **3** is explicable according to the previously proposed reaction path,[7] involving intermediate formation of **2** from **3** in the initial step.

Table 1. Cu-Promoted oxidative dimerization of skatoles **3**



Entry	**3**	Conditions[a]	Yield (%)[b] **1**	**2**
1	**3a** (R = H)	$CuBr_2 \cdot SMe_2$ (0.2 equiv), DABCO (1 equiv), in air	15 (**1a**)	40 (**2a**)
2	**3a** (R = H)	$Cu(OTf)_2$ (0.2 equiv), DABCO, in air	--- (**1a**)	72 (**2a**)
3	**3a** (R = H)	$CuBr_2 \cdot SMe_2$ (0.2 equiv), PCC (2 equiv)	14 (**1a**)	55 (**2a**)
4	**3a** (R = H)	$Cu(OAc)_2$ (0.2 equiv), PCC (2 equiv)	20 (**1a**)	50 (**2a**)
5	**3a** (R = H)	CuBr (0.2 equiv), PCC (2 equiv)	15 (**1a**)	45 (**2a**)
6	**3a** (R = H)	CuI (0.2 equiv), PCC (2 equiv)	30 (**1a**)	---
7	**3a** (R = H)	CuI (0.5 equiv), PCC (2 equiv)	37 (**1a**)	---
8	**3a** (R = H)	CuI (1.1 equiv), PCC (1 equiv)	22 (**1a**)	---
9	**3a** (R = H)	CuI (1.1 equiv), PCC (2 equiv)	52 (**1a**)	---
10	**3a** (R = H)	PCC (2 equiv)	---	20 (**2a**)[c]
11	**3b** (R = Me)	CuI (1.1 equiv), PCC (2 equiv)	33 (**1b**)	---
12	**3c** (R = OMe)	CuI (1.1 equiv), PCC (2 equiv)	30 (**1c**)	---
13	**3d** (R = Cl)	CuI (1.1 equiv), PCC (2 equiv)	27 (**1d**)	---

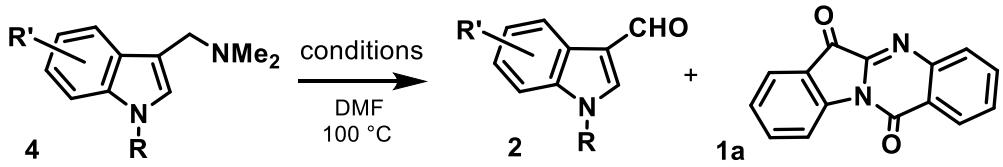
[a]All reactions were carried out in air. [b]Isolated yield. [c]**3a** was recovered in 50% yield.

Since 1-methyl-3-indolecarbaldehyde was also obtainable through the oxidation of 1-methylgramine,[8] we next examined whether gramine (**4a**) would tolerate the dimerization conditions (Table 2). First, **4a** was oxidized with CuI and PCC, although only trace amounts of **1a** were obtained, accompanied by the formation of significant amounts of **2a** (Entry 1). Trace conversion of **4a** to **1a** remained unaltered even in additional reactions, in which the formation of **2a** also predominated (Entries 2–4). Although **4a** did not tolerate the oxidative dimerization, heating **4a** with PCC (1.1 equiv) in DMF at 100 °C for 0.5 h afforded **2a** in 85% yield without the formation of **1a** (Entry 5). These conditions also worked for the oxidation of gramines **4b**–**4g**, producing corresponding aldehydes **2b**–**2h** in high yields (Entries 6–12).

In summary, during the present investigation of the oxidation of skatoles **3** and gramines **4**, a difference in the reaction outcome between **3** and **4** was observed. Thus, Cu-mediated oxidative dimerization of

skatoles **3** provided indoloquinazolones **1** in a one-pot reaction, which involved intermediate formation of aldehydes **2**. However, evaluation of the oxidation of gramines **4** showed that the oxidation of **4** predominantly produced aldehydes **2** instead of dimerization products **1**.[9]

Table 2. PCC oxidation of gramines **4**



Entry	**4**	Conditions[a]	Yield (%)[b] **1a**	Yield (%)[b] **2**
1	**4a** (R = R' = H)	CuI (1.1 equiv), PCC (2 equiv), 24 h	5	60 (**2a**)
2	**4a**	$CuBr_2 \cdot SMe_2$ (0.2 equiv), DABCO (1 equiv), 24 h	5	65 (**2a**)
3	**4a**	$CuBr_2 \cdot SMe_2$ (0.2 equiv), PCC (2 equiv), 24 h	5	63 (**2a**)
4	**4a**	CuBr (0.2 equiv), DABCO (1 equiv), 24 h	5	60 (**2a**)
5	**4a**	PCC (1.1 equiv), 0.5 h	---	85 (**2a**)
6	**4b** (R = Me, R' = H)	PCC (1.1 equiv), 0.5 h	---	89 (**2b**)
7	**4c** (R = OMe, R' = H)	PCC (1.1 equiv), 0.5 h	---	90 (**2c**)
8	**4d** (R = H, R' = 5-Me)	PCC (1.1 equiv), 0.5 h	---	90 (**2d**)
9	**4e** (R = H, R' = 5-OMe)	PCC (1.1 equiv), 0.5 h	---	90 (**2e**)
10	**4f** (R = H, R' = 5-Br)	PCC (1.1 equiv), 0.5 h	---	90 (**2f**)
11	**4g** (R = H, R' = 4-Br)	PCC (1.1 equiv), 0.5 h	---	80 (**2g**)
12	**4h** (R = H, R' = 7-Br)	PCC (1.1 equiv), 0.5 h	---	45 (**2h**)

[a]All reactions were carried out in air. [b]Isolated yield.

EXPERIMENTAL

Melting points were recorded with a Yamato MP21 and are uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference.

General procedure for the oxidation of 3: After a mixture of CuI (4.4 mmol) and PCC (8 mmol) in DMF (30 mL) was stirred at room temperature for 30 min, **3** (4 mmol) was then added to the mixture and the mixture was stirred at 100 °C for 24 h. After cooling, the resulting mixture was added to 10% aqueous HCl solution, extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with CH_2Cl_2 to give **1**.

Tryptanthrin (1a): Yellow solid. Mp 266-268 °C. IR ($CHCl_3$): 1728, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.42 (t, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.78 (td, *J* = 1.2, 7.5 Hz, 1H), 7.84 (td, *J* = 1.2, 8.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.41 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.60 (d, *J* = 8.0 Hz,

1H). ^{13}C-NMR ($CDCl_3$) δ: 118.1, 122.0, 123.8, 125.5, 127.3, 127.6, 130.3, 130.8, 135.2, 138.4, 144.4, 146.4, 146.7, 158.2, 182.7. HR-MS (ESI) *m/z*: Calcd for $C_{15}H_9N_2O_2$ [(M+H) $^+$]: 249.0664. Found: 249.0669.

2,8-Dimethylindolo[2,1-*b*]quinazoline-6,12-dione (1b): Yellow solid. Mp 251-253 °C. IR ($CHCl_3$): 1724, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (s, 3H), 2.54 (s, 3H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.89 (t, *J* = 8.1 Hz, 1H), 8.20 (s, 1H), 8.46 (d, *J* = 8.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 21.2, 21.7, 117.8, 122.2, 123.6, 125.5, 127.3, 130.6, 136.3, 137.4, 138.9, 141.2, 144.1, 144.4, 144.7, 158.1, 182.8. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{13}N_2O_2$ [(M+H)$^+$]: 277.0977. Found: 277.0977.

2,8-Dimethoxyindolo[2,1-*b*]quinazoline-6,12-dione (1c): Yellow solid. Mp 281-283 °C (EtOH). IR ($CHCl_3$): 1730, 1687 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 3H), 3.97 (s, 3H), 7.29 (dd, *J* = 2.9, 8.6 Hz, 1H), 7.36 (d, *J* = 3.5 Hz, 1H), 7.38 (dd, *J* = 2.9, 9.2 Hz, 1H), 7.80 (d, *J* = 2.9 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 8.49 (d, *J* = 9.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 56.1, 56.2, 108.2, 108.4, 119.2, 123.4, 124.2, 124.9, 125.4, 132.5, 140.3, 140.9, 143.1, 157.6, 158.8, 161.4, 182.6. HR-MS (ESI) *m/z*: Calcd for $C_{17}H_{12}N_2NaO_4$ [(M+Na)$^+$]: 331.0695. Found: 331.0693.

2,8-Dichloroindolo[2,1-*b*]quinazoline-6,12-dione (1d): Yellow solid. Mp 287-289 °C. IR ($CHCl_3$): 1736, 1689 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.75 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.80 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 8.57 (d, *J* = 8.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ: 119.4, 123.2, 124.9, 125.4, 127.3, 132.3, 133.7, 135.8, 137.1, 137.9, 144.1, 144.3, 145.1, 156.9, 181.2. HR-MS (ESI) *m/z*: Calcd for $C_{15}H_7Cl_2N_2O_2$ [(M+H)$^+$]: 316.9885, 318.9855. Found: 316.9882, 318.9843.

General procedure for the oxidation of 4: PCC (1.1 mmol) was added to a stirred solution of **4** (1 mmol) in DMF (5 mL) at 100 °C (pre-heated oil bath) and the mixture was stirred at 100 °C for 0.5 h. After cooling, the resulting mixture was added to 10% aqueous HCl solution, extracted with AcOEt (100 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with CH_2Cl_2 to give **2**.

1-Methylindole-3-carbaldehyde (2b): Colorless solid. Mp 69-70 °C. IR ($CHCl_3$): 1659 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (s, 3H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H), 9.86 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 33.9, 111.5, 117.5, 121.4, 123.0, 124.0, 125.1, 138.2, 142.1, 184.9. HR-MS (ESI) *m/z*: Calcd for $C_{10}H_9NNaO$ [(M+Na)$^+$]: 182.0582. Found: 182.0585.

1-Methoxyindole-3-carbaldehyde (2c): Colorless solid. Mp 50-51 °C. IR ($CHCl_3$): 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.19 (s, 3H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 8.30 (d, *J* = 7.4 Hz, 1H), 9.99 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 66.9, 108.8, 114.2, 121.8, 122.2, 123.6, 124.7, 131.8, 132.8, 184.2. HR-MS (ESI) *m/z*: Calcd for $C_{10}H_{10}NO_2$ [(M+H)$^+$]: 176.0712. Found:

176.0705.

5-Methyl-1*H*-indole-3-carbaldehyde (2d): Colorless solid. Mp 147-148 °C. IR ($CHCl_3$) δ: 3419, 1647, 1628 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.36 (s, 3H), 7.04 (dd, *J* = 1.7, 8.6 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H), 8.18 (s, 1H), 9.86 (s, 1H), 11.98 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 21.7, 112.6, 118.4, 121.1, 124.9, 125.5, 131.6, 135.9, 138.9, 185.4. HR-MS (ESI) *m/z*: Calcd for $C_{10}H_{10}NO$ [$(M+H)^+$]: 160.0762. Found: 160.0734.

5-Methoxy-1*H*-indole-3-carbaldehyde (2e): Colorless solid. Mp 182-183 °C. IR ($CHCl_3$): 3462, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.75 (s, 3H), 6.85 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 2.9 Hz, 1H), 8.17 (s, 1H), 9.86 (s, 1H), 11.99 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 55.8, 103.0, 113.7, 113.8, 118.6, 125.4, 132.3, 138.9, 156.2, 185.4. HRMS (ESI): calcd for $C_{10}H_9NNaO_2$ [$(M+Na)^+$]: 198.0531. Found 198.0494.

5-Bromo-1*H*-indole-3-carbaldehyde (2f): Colorless solid. Mp 204-206 °C. IR ($CHCl_3$): 3460, 3446, 1667 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.35 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 8.18 (s, 1H), 8.31 (s, 1H), 9.89 (s, 1H), 12.29 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 115.1, 115.4, 117.9, 123.5, 126.4, 126.6, 136.3, 139.8, 185.7. HR-MS (ESI) *m/z*: Calcd for $C_9H_6BrNNaO$ [$(M+Na)^+$]: 245.9530, 247.9510. Found: 245.9545, 247.9512.

4-Bromo-1*H*-indole-3-carbaldehyde (2g): Colorless solid. Mp 182-184 °C. IR ($CHCl_3$): 3447, 1657 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.14 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 8.27 (s, 1H), 10.64 (s, 1H), 12.55 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 112.8, 112.9, 118.3, 124.3, 125.2, 126.5, 134.4, 138.8, 185.1. HR-MS (ESI) *m/z*: Calcd for C_9H_7BrNO [$(M+H)^+$]: 223.9711, 225.9691. Found: 223.9694, 225.9725.

7-Bromo-1*H*-indole-3-carbaldehyde (2h): Colorless solid. Mp 169-171 °C. IR ($CHCl_3$): 3447, 1668 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.14 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 6.9 Hz, 1H), 8.06 (dd, *J* = 1.2, 8.1 Hz, 1H), 8.34 (s, 1H), 9.93 (s, 1H), 12.36 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 105.4, 119.4, 120.8, 124.2, 126.3, 126.7, 136.0, 139.6, 185.9. HR-MS (ESI) *m/z*: Calcd for C_9H_7BrNO [$(M+H)^+$]: 223.9711, 225.9691. Found: 223.9719, 225.9721.

ACKNOWLEDGEMENTS

This work was supported in part by the Ministry of Education, Culture, Sports, Sciences, and Technology of Japan through a Grant-in Aid for Scientific Research (No. 26460012).

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9. It was assumed that two-electron oxidation of **4a** formed iminium cation **A** in situ, where **A** was inert. Aldehyde **2a** resulted from hydrolysis of **A** after the reaction mixture was worked up.