IMIDAZOLE DERIVATIVES. PART II.[1]
SYNTHESIS OF IMIDAZO[1,2-a]PYRIDIN-5-ONES

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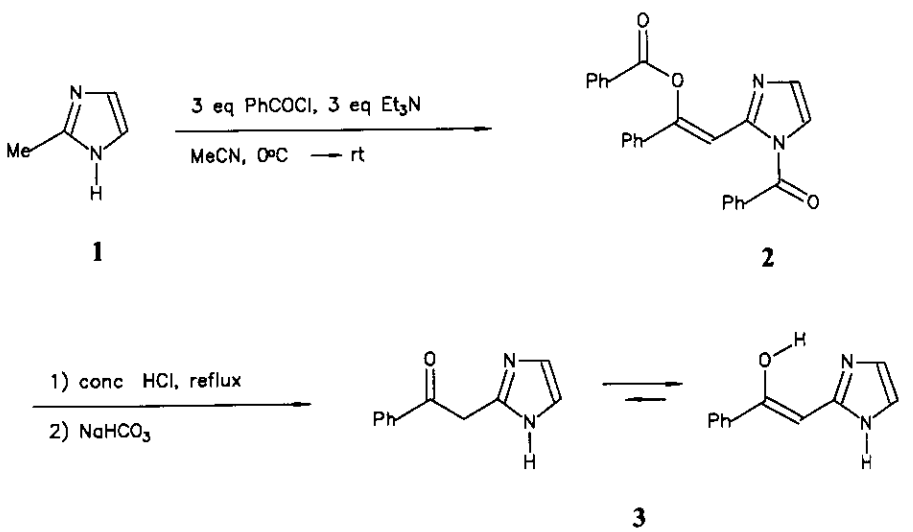
Abstract- The reaction of 2-phenacylimidazole with acetylenic esters provides imidazo[1,2-a]pyridin-5-ones by an one-pot procedure.

INTRODUCTION

In connection with our studies of the transacylations of acylimidazoles with activated alkynes we recently reported an imidazo[1,2-a]pyridine synthesis by a condensation reaction of 1-phenylacetylimidazole with acetylenic dicarboxylic esters[1]. Herein we describe a further novel pyridine cyclization providing imidazo[1,2-a]pyridin-5-ones.



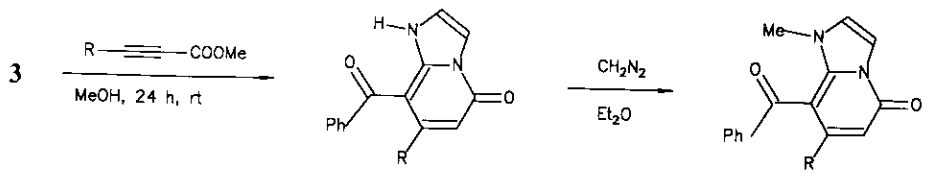
1 **2** **3**

Scheme 1.

The starting 2-phenacylimidazole (**3**) was prepared by a modification of a literature procedure.[2,3] Benzoylation of 2-methylimidazole (**1**) gives the enol benzoate (**2**), which on subsequent hydrolysis leads to (**3**) (Scheme 1).

PYRIDONE-CYCLIZATION

The 2-phenacylimidazole (**3**) reacts with acetylenic esters[4] (**a**: dimethyl acetylenedicarboxylate and **b**: methyl propiolate) in methanol at room temperature yielding the imidazo[1,2-a]pyridin-5-ones (**4**)[5] (Scheme 2). The compounds (**4**) are smoothly N-methylated to give (**5**)[5] by using diazomethane. The imidazo[1,2-a]pyridones (**4a**) and (**5a**) obtained by this method exhibit a very intense yellow colour.



a (R=COOMe) **4a** (80%) **5a** (94%)

b (R=H) **4b** (33%) **5b** (99%)

Scheme 2.

CRYSTAL STRUCTURE ANALYSIS

In order to give further confirmation of our structure assignments, which are in disagreement to previous ones[2,5], we determined the structure of the imidazo[1,2-a]pyridin-5-one (**5a**) by X-ray analysis[6] (Figure 1).

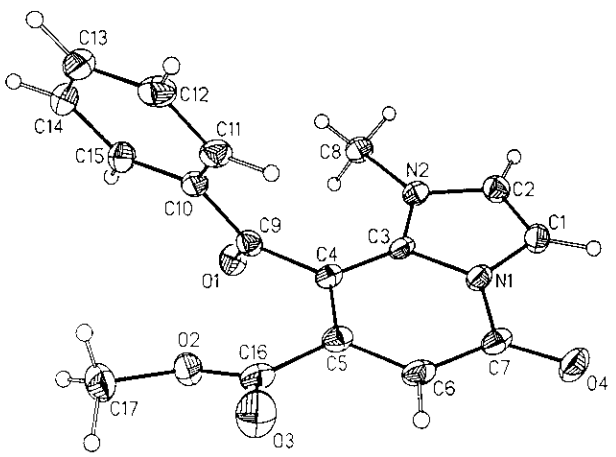
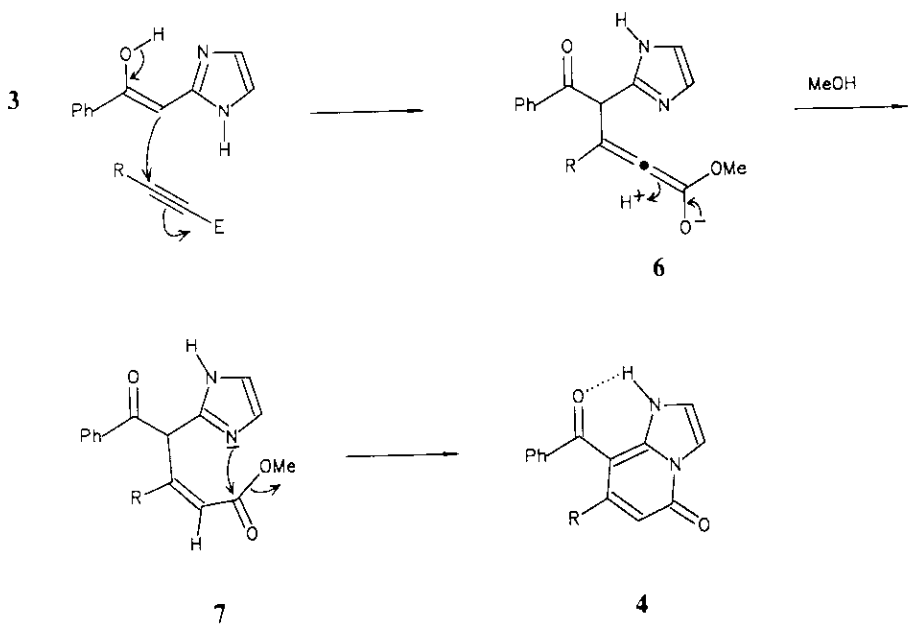


Figure 1.

Compound (**5a**) crystallizes in the monoclinic space group $P2_1/c$. Table 1 shows the atomic coordinates and equivalent isotropic displacement factors; bond lengths and bond angles are listed in Table 2 and 3 (see Experimental section). The imidazo[1,2-a]pyridine ring of **5a** is almost planar having only a slight twist of the imidazole ring plane relative to the pyridine ring plane (1.8°). Both carbonyl groups are not in conjugation with the pyridone system. The methyl ester carbonyl group is rotated out of the ring plane by 24.0° and the benzoyl carbonyl group by 64.6°.

MECHANISM

In agreement with known nucleophilic additions to acetylenic esters[4] we propose the following mechanism for this reaction (Scheme 3). Addition of **3** with its activated methylene group to the acetylene ester leads to the intermediate (**6**), which is externally protonated[7] by methanol to the trans addition product (**7**). Compound (**7**) is capable of cyclization via an intramolecular acylation by loss of methanol to the product (**4**). This mechanism is supported by the fact that the yield of **4** is considerably lower using acetonitrile as the solvent. According to their uv, ^{1}H-nmr, and ^{13}C-nmr spectra (see Experimental section) both **4a** and **4b** in solution exist exclusively in the pyridone form. Thus they are N-methylated to **5a** and **5b** with diazomethane.



Scheme 3.

CONCLUSION

In contrast to our first synthesis of the imidazo[1,2-a]pyridine framework this reaction results in an overall trans addition to the acetylene incorporating the carbonyl group of the methyl ester into the pyridine ring. Because of the different cyclization mode acetylenic esters having only one ester group at the triple bond such as methyl propiolate can also be used in this condensation. The only moderate yield of the cyclization with methyl propiolate is explained by the lower electrophilicity of this compound compared to DMAD.
The described procedure allows an easy access to the imidazo[1,2-a]pyridine ring system, several derivatives of which are of current interest as antiulcer agents[8].

EXPERIMENTAL

Uv spectra: Beckmann 3600; ir spectra: Perkin-Elmer 1710 (FTIR); ^{1}H-nmr spectra: Bruker WP-200 and ^{13}C-nmr spectra: Bruker AM-300, internal standard: tetramethylsilane or chloroform; mass spectra: Finnigan MAT-312, at an ionization potential of 70 eV; elemental analyses: Heraeus CHN-Rapid.

1-Benzoyl-2-(2-phenyl-2-benzoyloxyvinyl)imidazole (2)

Triethylamine (114 ml, 834 mmol) was added to a solution of 2-methylimidazole (1) (20 g, 244 mmol) in dry acetonitrile (380 ml). The solution was cooled to 0°C and benzoyl chloride (94 ml, 802 mmol) added dropwise under nitrogen. After the addition was completed the reaction mixture was stirred for 2 h at room temperature under nitrogen. The solvent was removed under reduced pressure, the residue was taken up in methylene chloride (800 ml) and washed with water (400ml). The organic layer was dried over magnesium sulfate and the solvent was removed in vacuo. The precipitated crystals were separated by filtration and washed with diethyl ether to afford **2** (66.5 g, 69%) as pale yellow crystals, mp 171-173°C (from benzene/petroleum ether); ir (KBr) ν_{max} 1786, 1737, 1713, 1599, 1450, 1384, 1289, 1244, 1087, 1068, 905, 708 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 6.92 (d, J = 1.6 Hz, 1 H), 7.08 (d, J = 1.6 Hz, 1 H), 7.34-7.68 (m, 12 H), 7.77-7.82 (m, 2 H), 8.25-8.30 (m, 2 H); ^{13}C-nmr (75 MHz, $CDCl_3$) δ 104.3 (d), 119.8 (d), 125.2 (d), 128.4 (d, 2 C), 128.6 (d, 2 C), 128.7 (d, 2 C), 129.4 (d), 129.7 (d, 2 C), 130.06 (d, 2 C), 130.14 (s), 130.4 (d, 2 C), 132.9 (s), 133.1 (d), 133.6 (d), 134.8 (s), 144.3 (s), 150.2 (s), 164.5 (s), 168.0 (s); ms (120°C) *m/z* (%) 394 (M^+, 2), 122 (3), 105 (8), 101 (25), 87 (100); hrms calcd for $C_{25}H_{18}N_2O_3$: 394.1317, found: 394.1318.

2-Phenacylimidazole (3)

The enol benzoate (**2**) (11.8 g, 30 mmol) was refluxed in conc. HCl (180 ml) for 1.5 h. After cooling the reaction mixture is diluted with H_2O (120 ml) and washed twice with benzene (150 ml) to remove benzoic acid. The aqueous solution was concentrated in vacuo and the residue was recrystallized from

ethanol/diethyl ether to yield the hydrochloride of **2** (4.65 g) as colourless crystals, mp 256-258°C. The hydrochloride of **2** (4.65 g, 20.9 mmol) was dissolved in H_2O (100 ml), neutralized with solid $NaHCO_3$ and extracted 3 times with methylene chloride (120 ml). The combined organic layers were dried over magnesium sulfate and the solvent evaporated. Recrystallization of the residue from diethyl ether gave **3** (3.74 g, 67%) as pale yellow crystals, mp 101-103°C; uv (MeOH) λ_{max} 320, 280, 243 nm; ir (KBr) ν_{max} 3200-2500, 1685, 1596, 1450, 1369, 1332, 1222, 1098, 999, 758, 740, 687 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 4.56 (s, br, 1 H), 7.03 (s, 2 H), 7.37-7.58 (m, 4 H), 7.98-8.02 (m, 2 H), 9.38 (s, br, 1 H); ms (80°C) *m/z* (%) 186 (M^+, 19), 185 (26), 158 (31), 105 (100); hrms calcd for $C_{11}H_{10}N_2O$: 186.0793, found: 186.0793. Anal. Calcd for $C_{11}H_{10}N_2O$·HCl: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.04; H, 4.94; N, 12.28.

Methyl 8-benzoyl-5-oxo-1H-imidazo[1,2-a]pyridine-7-carboxylate (4a)

DMAD (1.9 ml, 15 mmol) was added dropwise to a solution of 2-phenacylimidazole (2.79g, 15 mmol) in methanol (20 ml) at room temperature under nitrogen. After 24 h of stirring at the same temperature, the precipitate was collected by filtration and washed first with cold methanol and then with diethyl ether. Further crystals were obtained by concentration of the mother liquor to provide **4a** (3.57 g, 80%) as yellow crystals, mp 219-220°C; uv (MeOH) λ_{max} 373, 312, 245 nm; ir (KBr) ν_{max} 3268, 3139, 1734, 1670, 1605, 1520, 1457, 1356, 1327, 1265, 1102, 918, 741, 616 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 3.14 (s, 3 H), 6.32 (s, 1H), 7.18 (t, J = 2.3 Hz, 1 H), 7.41 - 7.61 (m, 5H), 7.86 (t, J = 2.3 Hz, 1H), 12.03 (s, broad, 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$) δ 52.2 (q), 96.5 (s), 104.0 (d), 110.4 (d), 117.7 (d), 127.8 (d, 2 C), 128.5 (d, 2 C), 131.4 (d), 140.8 (s), 143.8 (s, 2 C), 156.3 (s), 167.3 (s), 192.6(s); ms (190°C) *m/z* (%) 296 (M^+, 100), 295 (70), 264 (20), 263 (62), 237 (16), 236 (16), 235 (18), 219 (13), 208 (16). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.78; H, 4.18; N, 9.44.

8-Benzoyl-1H-imidazo[1,2-a]pyridin-5-one (4b)

Methyl propiolate (1.3 ml, 15 mmol) was added dropwise to a solution of 2-phenacylimidazole (2.80 g, 15 mmol) in methanol (20 ml) at room temperature under nitrogen. After 24 h of stirring at room temperature the precipitate was collected by filtration and washed with cold methanol and diethyl ether. The crystallization was completed by concentration of the mother liquor and addition of diethyl ether to give **4b** (1.17 g, 33%) as pale yellow crystals, mp 239-240°C; uv (MeOH) λ_{max} 348, 306, 239 nm; ir (KBr) ν_{max} 3140, 1680, 1599, 1565, 1536, 1373, 1336, 1223, 1086, 744, 714, 608 cm^{-1}; ^{1}H-nmr (200 MHz, DMSO-d_6) δ 5.84 (d, J = 9.3 Hz, 1 H), 7.51 - 7.66 (m, 6 H), 7.70 (d, J = 9.3 Hz, 1 H), 7.89 (d, J = 2.3 Hz, 1 H), 13.09 (s, broad, 1 H); ^{13}C-nmr (75 MHz, DMSO-d_6) δ 98.6 (s), 99.9 (d), 109.5 (d), 118.9 (d), 128.1 (d, 2 C), 128.2 (d, 2 C), 130.4 (d), 139.0 (s), 140.8 (d), 141.8 (s), 156.3 (s), 189.7 (s); ms (180°C) *m/z* (%) 238 (M^+, 98), 237

(100), 209 (20), 180 (28), 161 (30). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.52; H, 4.32; N, 11.68.

Methyl 8-benzoyl-1-methyl-5-oxoimidazo[1,2-a]pyridine-7-carboxylate (5a)

A solution of diazomethane in diethyl ether was added dropwise to a suspension of the imidazo[1,2-a]pyridone (**4a**) (740 mg, 2.5 mmol) in diethyl ether (10 ml). After 2.5 h of stirring at room temperature the solvent was evaporated and the residue was recrystallized from benzene to afford **5a** (727 mg, 94%) as yellow crystals, mp 185-186°C; uv (MeOH) λ_{max} 376, 245 nm; ir (KBr) ν_{max} 3143, 1722, 1672, 1641, 1515, 1448, 1259, 1013, 789, 723 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 3.39 (s, 3 H), 3.53 (s, 3H), 6.43 (s, 1H), 7.08 (d, J = 2.4 Hz, 1 H), 7.43 - 7.62 (m, 3 H), 7.81 - 7.86 (m, 2 H), 7.92 (d, J = 2.4 Hz, 1 H); ^{13}C-nmr (75 MHz; $CDCl_3$) δ 37.3 (q), 52.3 (q), 98.9 (s), 100.5 (d), 109.2 (d), 123.9 (d), 128.6 (d, 2 C), 129.0 (d, 2 C), 133.0 (d), 139.3 (s), 140.0 (s), 140.4 (s), 155.8 (s), 166.7 (s), 191.7 (s); ms (160°C) *m/z* (%) 310 (M^+, 100%), 279 (6), 251 (25), 233 (47), 223 (22), 205 (16). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.73; H, 4.54; N, 9.08.

8-Benzoyl-1-methylimidazo[1,2-a]pyridin-5-one (5b)

A solution of diazomethane in diethyl ether was added dropwise to a suspension of the imidazo[1,2-a]pyridone (**4b**) (476 mg, 2 mmol) in diethyl ether (10 ml). After 2.5 h of stirring at room temperature the solvent was removed and the residue was dried in vacuo to provide **5b** (499 mg, 99%) as a yellow foam; uv (MeOH) λ_{max} 349, 243 nm; ir (KBr) ν_{max} 2925, 1669, 1618, 1557, 1529, 1325, 1270, 1074, 1007, 879, 707 cm^{-1}; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 3.84 (s, 3 H), 5.96 (d, J = 9.3 Hz, 1 H), 7.08 (d, J = 2.4 Hz, 1 H), 7.45 - 7.64 (m, 3 H), 7.69 (d, J = 9.3 Hz, 1 H), 7.80 - 7.85 (m, 2 H), 7.94 (d, J = 2.4 Hz, 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$) δ 38.2 (q), 99.7 (d), 101.1 (s), 110.0 (d), 122.9 (d), 128.3 (d, 2 C), 129.8 (d, 2 C), 132.0 (d), 138.7 (s), 142.5 (s), 142.6 (d), 157.1 (s), 190.1 (s); ms (120°C) *m/z* (%) 252 (M^+, 100%), 222 (28), 194 (28), 174 (42); hrms calcd for $C_{15}H_{12}N_2O_2$: 252.0899, found: 252.0898.

X-ray analysis of (5a)

Data collection and calculations were carried out using a Nicolet R3m/V four-circle diffractometer with a MicroVAX II computer and SHELXTL-PLUS software[6].

Formula: $C_{17}H_{14}N_2O_4$, crystal size: 0.31 · 0.28 · 0.07 mm, monoclinic, space group $P2_1/c$, a=8.792(3), b=23.797(8), c=7.517(2) Å, $\alpha=\gamma=90°$, $\beta=114.91(2)°$, V=1426.3(8) $Å^3$, T=125 K, Z=4, ρ_{calcd}=1.445 g cm^{-3}, μ=0.1 mm^{-1}; $Mo_{K\alpha}$ radiation (graphite monochromator); scan range $3° \leq 2\theta \leq 50°$; independent reflections 2544, observed 2224 ($F_o \geq 4\sigma(F)$), R=0.046, R_w=0.047.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement factors ($Å^2 \times 10^4$)

	x	y	z	U_{eq}
O(1)	3350(2)	3658(1)	11418(2)	244(5)*
O(2)	1184(2)	2948(1)	7557(2)	234(5)*
O(3)	-550(2)	3125(1)	4426(2)	377(6)*
O(4)	-2344(2)	5119(1)	5071(2)	275(5)*
N(1)	178(2)	4974(1)	7665(2)	186(6)*
N(2)	2600(2)	5001(1)	10225(2)	190(6)*
C(1)	423(2)	5521(1)	8365(3)	217(7)*
C(2)	1896(2)	5531(1)	9926(3)	220(7)*
C(3)	1527(2)	4651(1)	8819(3)	175(7)*
C(4)	1623(2)	4084(1)	8412(3)	182(6)*
C(5)	264(2)	3878(1)	6734(3)	199(7)*
C(6)	-1100(2)	4207(1)	5598(3)	216(7)*
C(7)	-1222(2)	4780(1)	5979(3)	207(7)*
C(8)	4219(2)	4863(1)	11834(3)	227(7)*
C(9)	3104(2)	3741(1)	9718(3)	189(7)*
C(10)	4312(1)	3539(1)	8938(2)	201(7)*
C(11)	4113	3668	7042	220(7)*+
C(12)	5261	3467	5361	267(8)*+
C(13)	6609	3136	7576	307(9)*+
C(14)	6808	3007	9472	310(8)*+
C(15)	5660	3208	10153	263(8)*+
C(16)	238(2)	3281(1)	6078(3)	227(7)*
C(17)	1586(3)	2396(1)	7051(3)	291(8)*

* *Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor*

\+ *Atoms in rigid groups have standard deviations only for the pivot atom.*

Table 2. Bond lengths (Å)

O(1)-C(9)	1.219 (3)	O(2)-C(16)	1.334 (2)
O(2)-C(17)	1.450 (3)	O(3)-C(16)	1.199 (2)
O(4)-C(7)	1.235 (2)	N(1)-C(1)	1.386 (2)
N(1)-C(3)	1.373 (2)	N(1)-C(7)	1.421 (2)
N(2)-C(2)	1.380 (2)	N(2)-C(3)	1.365 (2)
N(2)-C(8)	1.466 (2)	C(1)-C(2)	1.332 (2)
C(3)-C(4)	1.394 (3)	C(4)-C(5)	1.411 (2)
C(4)-C(9)	1.499 (2)	C(5)-C(6)	1.385 (2)
C(5)-C(16)	1.499 (3)	C(6)-C(7)	1.406 (3)
C(9)-C(10)	1.493 (3)		

Table 3. Bond angles (°)

C(16)-O(2)-C(17)	117.1(2)	C(1)-N(1)-C(3)	109.4(1)
C(1)-N(1)-C(7)	125.6(1)	C(3)-N(1)-C(7)	125.1(2)
C(2)-N(2)-C(3)	108.4(1)	C(2)-N(2)-C(8)	123.5(1)
C(3)-N(2)-C(8)	128.0(1)	N(1)-C(1)-C(2)	106.8(2)
N(2)-C(2)-C(1)	109.3(2)	N(1)-C(3)-N(2)	106.1(1)
N(1)-C(3)-C(4)	121.3(1)	N(2)-C(3)-C(4)	132.5(1)
C(3)-C(4)-C(5)	115.2(1)	C(3)-C(4)-C(9)	119.9(1)
C(5)-C(4)-C(9)	124.9(2)	C(4)-C(5)-C(6)	122.8(2)
C(4)-C(5)-C(16)	120.9(1)	C(6)-C(5)-C(16)	116.3(1)
C(5)-C(6)-C(7)	122.9(2)	O(4)-C(7)-N(1)	118.0(2)
O(4)-C(7)-C(6)	129.3(2)	N(1)-C(7)-C(6)	112.7(1)
O(1)-C(9)-C(4)	119.7(2)	O(1)-C(9)-C(10)	121.2(1)
C(4)-C(9)-C(10)	118.9(2)	C(9)-C(10)-C(11)	121.7(1)
C(9)-C(10)-C(15)	118.3(1)	O(2)-C(16)-O(3)	124.3(2)
O(2)-C(16)-C(5)	111.9(2)	O(3)-C(16)-C(5)	123.9(2)

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5. The structures of the compounds **4a**, **4b**, and **5a** have been assigned wrong before[2], which was already revealed in our previous paper[1].
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