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A CONVENIENT SYNTHESIS OF 3-BENZOYLINDOLIZINE-5-CARBALDEHYDES

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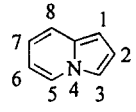
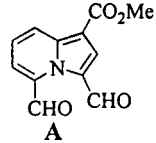
Abstract: 3-Benzoylindolizine-5-carbaldehydes (**4a-f**), which could be used as derivatization reagents for amino compounds in HPCE were synthesized based on the 1,3-dipolar cycloaddition of 1-phenacyl-2-(1,3-dioxolan-2-yl)pyridinium ylide with alkenes in the presence of TPCD.

For both of theoretical[1] and practical[2] reasons, many kinds of indolizines with special functions were designed and synthesized. Very recently, S. Oguri and his co-workers[3] recommended 1-methoxycarbonylindolizine-5-carbaldehyde (**A**) as a derivatization reagent for amino compounds in HPCE (high-performance capillary electrophoresis). Preparation of compound **A** was based on 1,3-dipolar cycloaddition of 1-(*tert*-butoxycabonylmethyl)-2-(1,3-dioxolan-2-yl)pyridinium ylide and methyl propiolate. According to the working mechanism, the aldehyde group at 5-position in compound **A** react with amine to yield Schiff base and the aldehyde at 1-position should stabilize the Schiff base. We have designed a series of 3-benzoylindolizine-5-carbaldehydes (**4**), which could be used as derivatization reagent for amino compounds in HPCE. Herein we report a convenient procedure for their preparations.



Indolizine



A

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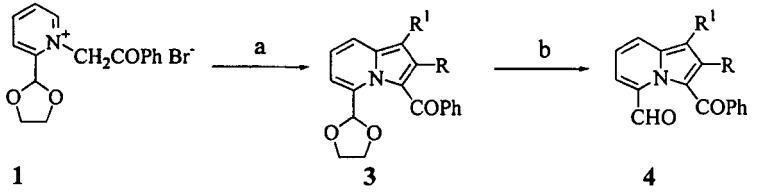
The methods for preparation of indolizine were summarized in several reviews[4] and some new procedures were reported recently[5]. Among them, 1,3-dipolar cycloaddition is one of important methods and usually carried out between pyridinium ylides and acetylenes. However, the method is limited seriously by using acetylenes as dipolarophiles, because the most of them are not commercially available.

In our previous work[6], a convenient and practical procedure was developed for 1,3-dipolar cycloaddition by using alkylenes instead of acetylenes in the presence of a versatile oxidant TPCD [tetrakispyridine cobalt(II) dichromate]. When the mixture of 1-phenacyl-2-(1,3-dioxolan-2-yl)pyridinium bromide (**1**), acrylonitrile (**2a**), TPCD and triethyl amine in DMF was heated for 4 h, 3-benzoyl-1-cyano-5-(1,3-dioxolan-2-yl)indolizine (**3a**) was obtained smoothly in 71% yield. Then **3a** was hydrolyzed in a solution of 10% aqueous HCl and THF to give their corresponding aldehyde (**4a**) in almost quantitative yield. By the same procedure, **3b-f** and **4b-f** were prepared in moderate to high yields (scheme 1 and table 1). The applications of **4a-f** as derivatization reagents for amino compounds in HPCE is under investigation and will be reported soon.

Scheme 1



1 3 4

Reagents and conditions: a. RCH=CHR^1(**2**)/TPCD/NEt$_3$/DMF/80-90 °C/2-4 h/61-73%. b. 10% aq. HCl/THF/reflux/1-3 h/96-99%.

Table 1. Indolizines **3a-f** and **4a-f** prepared

2,3,4	R	R	Yields (%) 3	4	2,3,4	R	R	Yields (%) 3	4
a	H	CN	71	99	**d**	H	COPh	70	99
b	H	CO_2Me	73	99	**e**	CO_2Me	CO_2Me	61	97
c	H	COMe	65	98	**f**	CO_2Et	CO_2Et	68	96

EXPERIMENTAL SECTION

Melting points were determined on a Yanco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. ^{1}H NMR spectra were recorded on a Bruker ACF-500 spectrometer using $CDCl_3$ as solvent and TMS as internal reference. *J* values are given in Hz. Mass spectra were obtained on a ZAB-HS mass spectrometer with 70 ev. Elemental analyses were performed on a Perkin-Elmer 240C instrument. TPCD[7] and 2-(1,3-dioxolan-2-yl)pyridine[8] were prepared by the known procedures.

Preparation of 1-phenacyl-2-(1,3-dioxolan-2-yl)pyridinium bromide (1): A mixture of 2-(1,3-dioxolan-2-yl)pyridine (15.1 g, 100 mmol) and phenacyl bromide (19.9 g, 100 mmol) in ethyl acetate (80 mL) was stirred at room temperature 12 h and then at 50-60 °C for 5 h. The solid was filtered and washed with ethyl acetate (3 x 5 mL) to give salt **1** (33.6 g, 96%) as yellow solids, mp 212-4 °C; IR: 1688, 1630, 1598, 1582, 1450, 1352, 1227, 1122, 784, 741, 698 cm^{-1}. It was used in next step directly without any further purification.

3-Benzoyl-1-cyano-5-(1,3-dioxolan-2-yl)indolizine (3a): A mixture of salt **1** (3.5 g, 10 mmol), acrylonitrile (**2a**) (1.6 g, 30 mmol), TPCD (5.9 g, 10 mmol) and triethylamine (1.0 g, 10 mmol) in DMF (80 mL) was stirred at 80-90 °C for 3 h (monitored by TLC). Then it was cooled to room temperature and 5% aqueous hydrochloric acid (150 mL) was added. The precipitate was collected by centrifugal separation and was purified by chromatography [silica gel, 25% EtOAc in petroleum ether (60-90°)] to give **3a** as yellowish needles, mp 128 °C; IR: 2214, 1645, 1595, 1518, 1483, 1349, 1230, 1159, 1124, 1096, 787, 716 cm^{-1}; ^{1}H NMR: δ 3.72 (t, *J* 7.1, 2H, OCH_2), 3.89 (t, *J* 7.1, 2H, OCH_2), 6.65 (s, 1H, OCHO), 7.38-7.55 (m, 5H, C_2-, C_6-, C_7-H, PhH), 7.65 (t, *J* 7.7, 1H, PhH), 7.83 (m, 1H, C_8-H), 7.96 (d, *J* 7.7, 2H, PhH) ppm; MS (*m/z*): 318 (M^+, 31), 245 (100), 219 (3), 213 (17), 105 (45), 77 (46). Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.56; H, 4.57; N, 8.73. By the same procedure (2-4 h, monitored by TLC), compounds **3b-f** were prepared.

Methyl 3-benzoyl-5-(1,3-dioxolan-2-yl)indolizine-1-carboxylate (3b): yellowish crystals, mp 139-40 °C; IR: 1701, 1623, 1574, 1518, 1476, 1342, 1223, 744, 716 cm^{-1}; ^{1}H NMR: δ 3.72 (t, *J* 6.2, 2H, OCH_2), 3.87-3.91 (m, 5H, OCH_2 and OCH_3), 6.71 (s, 1H, OCHO), 7.40-7.44 (m, 2H, C_6- and C_7-H), 7.52 (t, *J* 7.6, 2H, PhH), 7.59-7.63 (m, 2H, C_2-H and PhH), 7.99 (d, *J* 7.6, 2H, PhH), 8.47 (d, *J* 7.9, 1H, C_8-H) ppm; MS (*m/z*): 351 (M^+, 29), 320 (5), 292 (3), 278 (100), 274 (2), 246 (19), 105 (47), 77 (30). Anal. Calcd. for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.46; H, 4.87; N, 4.05.

1-Acetyl-3-benzoyl-5-(1,3-dioxolan-2-yl)indolizine (3c): yellowish crystals, mp 143-5 °C; IR: 1632, 1618, 1592, 1502, 1480, 1416, 1220, 1159,

1102, 738, 720 cm^{-1}; ^1H NMR: δ 2.48 (s, 3H, CH_3), 3.69 (t, *J* 6.7, 2H, OCH_2), 3.88 (t, *J* 6.7, 2H, OCH_2), 6.70 (s, 1H, OCHO), 7.45-7.56 (m, 5H, C_2-, C_6-, C_7-H, PhH), 7.64 (d, *J* 7.5, 1H, PhH), 8.01 (d, *J* 7.5, 2H, PhH), 8.72 (d, *J* 8.5, 1H, C_8-H) ppm; MS (*m/z*): 335 (M^+, 40), 292 (24), 262 (100), 258 (13), 230 (14), 105 (74), 77 (66). Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 4.89; N, 4.39. Found: C, 71.46; H, 4.86; N, 4.39.

1,3-Dibenzoyl-5-(1,3-dioxolan-2-yl)indolizine (3d): yellowish crystals, mp 122-4 °C; IR: 1614, 1609, 1599, 1503, 1482, 1428, 1342, 1243, 1212, 1159, 1100, 792, 718 cm^{-1}; ^1H NMR: δ 3.71 (t, *J* 7.7, 2H, OCH_2), 3.89 (t, *J* 7.7, 2H, OCH_2), 6.72 (s, 1H, OCHO), 7.39-7.69 (m, 9H, C_2-, C_6-, C_7-H, PhH), 7.79 (d, *J* 7.4, 2H, PhH), 7.99 (d, *J* 7.4, 2H, PhH), 8.73 (d, *J* 8.6, 1H, C_8-H) ppm; MS (*m/z*): 397 (M^+, 40), 324 (100), 292 (19), 105 (36), 77 (25). Anal. Calcd. for $C_{25}H_{19}NO_4$: C, 75.55; H, 4.82; N, 3.52. Found: C, 75.52; H, 4.97; N, 3.64.

Dimethyl 3-benzoyl-5-(1,3-dioxolan-2-yl)indolizine-1,2-dicarboxylate (3e): white crystals, mp 134 °C; IR: 1737, 1700, 1639, 1600, 1516, 1490, 1444, 1364, 1225, 1160, 1110, 1090, 799, 741 cm^{-1}; ^1H NMR: δ 3.25 (s, 3H, OCH_3), 3.67 (t, *J* 7.0, 2H, OCH_2), 3.83 (t, *J* 7.0, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 6.36 (s, 1H, OCHO), 7.37-7.41 (m, 2H, C_6- and C_7-H), 7.46 (t, *J* 7.5, 2H, PhH), 7.58 (t, *J* 7.5, 1H, PhH), 7.87 (d, *J* 7.7, 2H, PhH), 8.43 (d, *J* 7.4, 1H, C_8-H) ppm; MS (*m/z*): 409 (M^+, 21), 378 (25), 336 (100), 304 (35). Anal. Calcd. for $C_{22}H_{19}NO_7$: C, 64.54; H, 4.68; N, 3.42. Found: C, 64.64; H, 4.71; N, 3.25.

Diethyl 3-benzoyl-5-(1,3-dioxolan-2-yl)indolizine-1,2-dicarboxylate (3f): yellowish crystals, mp 145-6 °C; IR: 1729, 1694, 1644, 1595, 1518, 1497, 1448, 1363, 1230, 1117, 787, 695 cm^{-1}; ^1H NMR: δ 1.03 (t, *J* 7.1, 3H, CH_3), 1.31 (t, *J* 7.1, 3H, CH_3), 3.62-3.68 (m, 4H, OCH_2), 3.79-3.84 (m, 2H, OCH_2), 4.32 (q, *J* 6.9, 2H, OCH_2), 6.37 (s, 1H, OCHO), 7.37-7.47 (m, 4H, C_6-, C_7-H, PhH), 7.57 (t, *J* 7.7, 1H, PhH), 7.90 (d, *J* 7.7, 2H, PhH), 8.47 (d, *J* 7.8, 1H, C_8-H) ppm; MS (*m/z*): 437 (M^+, 39), 392 (52), 364 (100), 105 (68), 77 (40). Anal. Calcd. for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found: C, 65.94; H, 5.29; N, 3.30.

Preparation of 3-benzoyl-1-cyanoindolizine-5-carbaldehyde (4a): A solution of **3a** (0.6 g, 1.9 mmol) in THF (20 mL) was treated by 10% aqueous hydrochloric acid (1.0 mL) and the mixture was refluxed for 5 h (monitored by TLC). The solvent was removed on a rotavaper to give the crude product as a solid, which was purified by chromatography [silica gel, 25% EtOAc in petroleum ether (60-90°)] to give **4a** (0.5 g, 99%) as yellow needles, mp 149-50 °C; IR: 2221, 1701, 1616, 1574, 1476, 1349, 1237, 772, 716 cm^{-1}; ^1H NMR: δ 7.55-7.60 (m, 4H, C_7-H, PhH), 7.65-7.69 (m, 2H, C_2-, C_6-H), 8.01 (d, *J* 7.8, 2H, PhH), 8.05 (d, *J* 8.8, 1H, C_8-H), 9.88 (s, 1H, CHO) ppm; MS (*m/z*): 274 (M^+, 22), 245 (47), 169 (45), 105 (54), 77 (100). Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.68; N, 10.22. Found: C, 74.28; H, 3.80; N, 10.16. By the same procedure (4-6 h, monitored by TLC), compounds **4b-f** were prepared.

3-Benzoyl-1-methoxycarbonylindolizine-5-carbaldehyde (4b): yellowish crystals, mp 156-158 °C; IR: 1715, 1699, 1620, 1574, 1519, 1476, 1438, 1417, 1349, 1245, 1224, 773, 735, 708 cm^{-1}; ^1H NMR: δ 3.91 (s, 3H, OCH_3), 7.54-7.66 (m, 5H, C_6-, C_7-H and PhH), 7.80 (s, 1H, C_2-H), 8.02 (d, *J* 7.5, 2H, PhH), 8.63 (d, *J* 8.8, 1H, C_8-H), 9.87 (s, 1H, CHO) ppm; MS (*m/z*): 307 (M^+, 45), 279 (100), 278 (62), 248 (61), 202 (28), 105 (23), 77 (25). Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.38; H, 4.58; N, 4.90.

1-Acetyl-3-benzoylindolizine-5-carbaldehyde (4c): yellowish crystals, mp 125-6 °C; IR: 1692, 1660, 1612, 1572, 1508, 1474, 1411, 1243, 1228, 1165, 769, 719 cm^{-1}; ^1H NMR: δ 2.55 (s, 3H, CH_3), 7.57-7.69 (m, 6H, C_2-, C_6-, C_7-H, PhH), 8.04 (d, *J* 7.8, 2H, PhH), 8.88 (d, *J* 8.5, 1H, C_8-H), 9.85 (s, 1H, CHO) ppm; MS (*m/z*): 291 (M^+, 30), 262 (39), 248 (100), 105 (32), 77 (46). Anal. Calcd. for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.23; H, 4.68; N, 5.00.

1,3-Dibenzoylindolizine-5-carbaldehyde (4d): yellowish crystals, mp 134-6 °C; IR: 1691, 1623, 1610, 1572, 1500, 1495, 1404, 1342, 1250, 1220, 1153, 779, 712 cm^{-1}; ^1H NMR: δ 7.48-7.69 (m, 9H, C_2-, C_6-, C_7-H, PhH), 7.82 (d, *J* 7.5, 2H, PhH), 8.02 (d, *J* 7.7, 2H, PhH), 8.84 (d, *J* 8.5, 1H, C_8-H), 9.87 (s, 1H, CHO) ppm; MS (*m/z*): 353 (M^+, 65), 325 (100), 324 (74), 248 (82), 105 (10), 77 (10). Anal. Calcd. for $C_{23}H_{15}NO_3$: C, 78.17; H, 4.28; N, 3.96. Found: C, 77.94; H, 4.16; N, 4.28.

3-Benzoyl-1,2-dimethoxybonylindolizine-5-carbaldehyde (4e): yellow crystals, mp 234-5 °C; IR: 1739, 1682, 1646, 1498, 1500, 1448, 1380, 1333, 1260, 1221, 1208, 1064, 1092, 800, 732, 681 cm^{-1}; ^1H NMR: δ 3.34 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.48-7.52 (m, 3H, C_7-H, PhH), 7.60-7.63 (m, 2H, C_6-H, PhH), 7.93 (d, *J* 7.7, 2H, PhH), 8.68 (d, *J* 9.1, 1H, C_8-H), 9.70 (s, 1H, CHO) ppm; MS (*m/z*): 365 (M^+, 37), 336 (100), 334 (30), 306 (15), 288 (10). Anal. Calcd. for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83. Found: C, 65.79; H, 4.23; N, 3.71.

3-Benzoyl-1,2-diethoxybonylindolizine-5-carbaldehyde (4f): yellowish crystals, mp 158-9 °C; IR: 1736, 1687, 1659, 1595, 1497, 1455, 1384, 1258, 1223, 1166, 1089, 794, 730, 659 cm^{-1}; ^1H NMR: δ 1.03 (t, *J* 7.2, 3H, CH_3), 1.35 (t, *J* 7.2, 3H, CH_3), 3.74 (q, *J* 7.2, 2H, OCH_2), 4.36 (q, *J* 7.2, 2H, OCH_2), 7.48-7.51 (m, 3H, C_7-H, PhH), 7.58-7.63 (m, 2H, C_6-H, PhH), 7.96 (d, *J* 7.6, 2H, PhH), 8.70 (d, *J* 9.0, 1H, C_8-H), 9.63 (s, 1H, CHO) ppm; MS (*m/z*): 393 (M^+, 71), 364 (67), 348 (53), 320 (19), 288 (27), 105 (100), 77 (94). Anal. Calcd. for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.36; H, 5.01; N, 3.84.

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