Reaction of 1-Alkylthioisoquinolinium Salts with Active Methylene Compounds

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2-Alkyl-1-alkylthioisoquinolinium salts were readily prepared from 2-alkyl-1(2*H*)-isoquinolones *via* 2-alkyl-1(2*H*)-thioisoquinolones in two steps. Under mild conditions, the reaction of 2-alkyl-l-alkylthioisoquinolinium salts with active methylene compounds in the presence of sodium hydride afforded 2-alkyl-1-(substituted methylene)iso-quinolines in good yields. Pyrrolo[2,1-*a*]isoquinolines were synthesized by the cyclization of 2-benzyl-1-(substituted methylene)isoquinolines using acetic anhydride.

Key words cyclization; pyrrolo[2,1-*a*]isoquinoline; dimethyl malonate; methylthioisoquinolinium salt; active methylene compound

We have previously reported on the reaction of 2-methylthioquinolinium salts with active methylene compounds for the formation of a carbon–carbon bond.[1)] Additionally, various methods for the synthesis of indolizine derivatives have been reported.[2)] In view of the recent report by Iwao and Kuraishi.[2)] on the novel total synthesis of the marine alkaloid lamellarins, which contain the pyrrolo[2,1-*a*]isoquinoline skeleton (Chart 1),[3)] functionalized pyrrolo-[2,1-*a*]isoquinolines would function as very useful synthetic intermediates toward their syntheses. The conventional methods for preparing the substituted pyrrolo[2,1-*a*]isoquinoline derivatives are either *via* Michael condensation of Reissert compounds,[4)] or *via* 1,3- and 1,5-dipolar cycloaddition reactions.[5,6)] In this paper, we report a novel method for the synthesis of a pyrrolo[2,1-*a*]isoquinoline skeleton using the cyclization of 2-benzyl-1-(substituted methylene) isoquinolines, which are readily prepared by the reaction of 2-benzyl-1-alkylthioisoquinolinium iodides with active methylene compounds.

Reaction of 1-Alkylthioisoquinolinium Iodides with Active Methylene Compounds Initially, the reaction of active methylene compounds with isoquinolinium salts that have a methylthio group as a leaving group at the 1-position was examined under mild conditions in the presence of sodium hydride (Chart 2, Table 1). 2-Methyl- and 2-benzyl-1(2*H*)-thioisoquinolones (**3**,[7)] **4**) were prepared from 2-methyl- and 2-benzyl-1(2*H*)-isoquinolones (**1**,[8)] **2**) in excellent yields, respectively. The reaction of thioisoquinolones (**3**, **4**) with methyl iodide (**5a**) afforded 2-methyl- and 2-benzyl-1-methylthioisoquinolinium iodides (**6a**,[9)] **7**) in 99 and 77% yields, respectively. The reactions of **6a** with straight-chain active methylene compounds (**8a**—**c**) in the presence of sodium hydride for 1.5 h at room temperature afforded 2-methyl-1-(substituted methylene)isoquinolines (**9a**, 88%; **9b**, 81%; **9c**, 85%, respectively) in high yields. However, reactions of **6a** with straight-chain active methylene compounds (**8d**—**f**) afforded **9d**—**f** in moderate yields. Reactions of **6a** with cyclic active methylene compounds (**8g**, **h**) at 90 °C for 3 h gave 2-methyl-1-(substituted methylene)isoquinolines (**9g**, **h**) in 92% and 61% yields, respectively. Similarly, the reaction of **7** with **8a**—**e** produced 2-benzyl-1-(substituted methylene)-isoquinolines (**10a**, 95%; **10b**, 98%; **10c**, 99%; **10d**, 88%; **10e**, 53%, respectively). To examine the effects of the alkylthio group at the 1-position, the experiments were repeated using other alkyl iodides. In comparison to methyl iodide, the reaction of **3** with ethyl iodide (**5b**) and isopropyl iodide (**5c**) afforded low yields of the corresponding 1-alkylthioisoquinolinium salts (**6b**, 75%; **6c**, 52%). Furthermore, the reactions of **6b**, **c** with **8a** and with **8g** gave products [**9a** (65%, 65%); **9g** (42%, 40%)] in lower yields than that of **6a** with **8a**, **g** (Table 1). These results can be explained by assuming that the enol form arising from the active methylenes (**8d**—**f**) would be more stable than the corresponding keto form, and would tend to lower the yields. The reactions of **7** with bulky methylene compounds (**8f**—**h**) did not give the desired products (**10f**—**h**), whereas reactions of **6a** bearing a smaller methyl group at the 2-position proceeded with **8f**—**h**; hence it can be implied that steric hindrance between two bulky groups, specifically, 2-benzyl and phenyl in **8f** or alicyclic rings (**8g**, **h**) was a main factor in reducing the yield. Spectroscopic studies of compound **10b** showed nuclear Overhauser and exchange spectroscopy (NOE) correlations between the methyl of the ester and the 2-methylene groups, and therefore their configuration is suggested to be the Z-form. Unfortunately, similar NOE correlations were not observed between the ester and the 2-substituent groups of **9b**, **d**, and **10d**. In summary, this type of reaction is a promising method to form a carbon-carbon bond at the 1-position of an isoquinoline ring.

Synthesis of Pyrrolo[2,1-*a*]isoquinolines Our next step was cyclization of the 2-benzyl compounds (**10a**—**e**) in acetic anhydride to provide the functionalized pyrrolo[2,1-*a*]isoquinoline derivatives (Chart 3). Heating of **10a**, **d**, **e** in acetic anhydride at 130 °C for 4 h afforded the corresponding pyrrolo[2,1-*a*]isoquinolines (**11a**, 91%; **11b**, 88%; **11c**, 68%; respectively). Unfortunately, cyclizations of **10b**, **c** were unsuccessful, although **10b**, **c** were recovered. The structures of **11a**—**c** were determined as follows. ^{1}H-NMR spectra of **11a**—**c** showed that the signals (5.55—5.94 ppm) due to

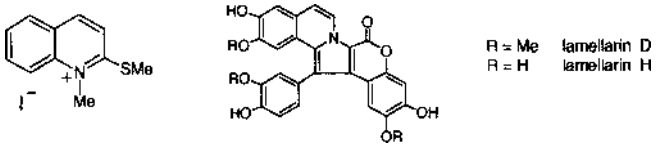

Chart 1

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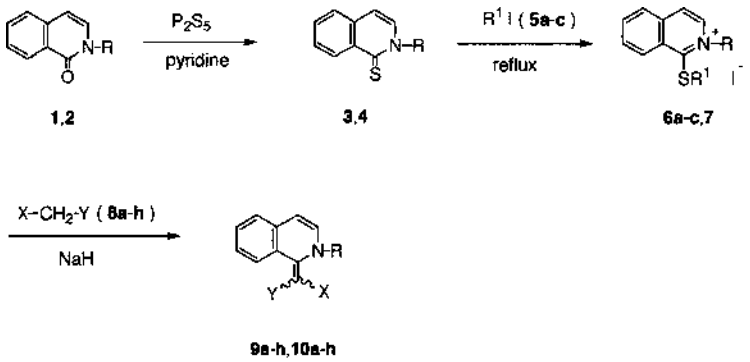

Chart 2

Table 1. Reaction of Isoquinolinium Salts with Active Methylene Compounds

Entry	Salt	Temp (°C)	Time (h)	Solvent	8a—h		Product	Yield (%)
					X	Y		
1	**6a**	rt[a)]	1.5	THF	COOMe	COOMe	**9a**	97
2	**6a**	rt	1.5	THF	CN	COOMe	**9b**	81
3	**6a**	rt	1.5	THF	CN	CN	**9c**	85
4	**6a**	rt	1.5	THF	COMe	COOMe	**9d**	69
5	**6a**	rt	1.5	THF	COMe	COMe	**9e**	47
6	**6a**	rt	1.5	THF	PhCO	COOEt	**9f**	49
7	**6a**	90	3	DMF	$COCH_2CH_2CH_2CO$		**9g**	92
8	**6a**	90	3	DMF	$COCH_2CH_2CO$		**9h**	61
9	**7**	rt	2	THF	COOMe	COOMe	**10a**	95
10	**7**	rt	2	THF	CN	COOMe	**10b**	98
11	**7**	rt	2	THF	CN	CN	**10c**	99
12	**7**	rt	2	THF	COMe	COOMe	**10d**	88
13	**7**	rt	2	THF	COMe	COMe	**10e**	53
14	**7**	rt	2	THF	PhCO	COOEt	**10f**	0
15	**7**	90	3	DMF	$COCH_2CH_2CH_2CO$		**10g**	0
16	**7**	90	3	DMF	$COCH_2CH_2CO$		**10h**	0
17	**6b**	rt	1.5	THF	COOMe	COOMe	**9a**	65
18	**6c**	rt	1.5	THF	COOMe	COOMe	**9a**	59
19	**6b**	90	3	DMF	$COCH_2CH_2CH_2CO$		**9g**	42
20	**6c**	90	3	DMF	$COCH_2CH_2CH_2CO$		**9g**	40

a) Room temperature.

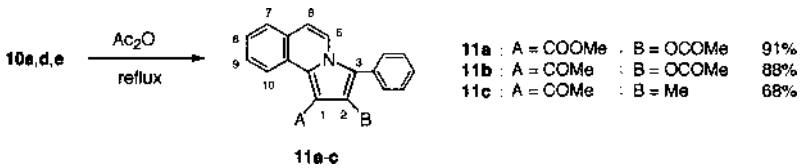

Chart 3

methylenes of benzyl groups in **10a**, **d**, **e** disappeared by dehydration and condensation.

In conclusion, we found that a novel reaction of active methylene compounds with isoquinolinium salts having a methylthio group as a leaving group at the 1-position gave 2-alkyl-1-(substituted methylene)isoquinolines under mild condition in fairly good yields. Cyclization of 2-benzyl compounds having an ester or an acetyl group in acetic anhydride produced the pyrrolo[2,1-*a*]isoquinolines in excellent yields.

Experimental

The following instruments were used to obtain physical data: Melting points, Yanaco micromelting point apparatus (values are uncorrected); IR spectra, Perkin-Elmer ET-IR1725X spectrometer; MS, JEOL JMN-DX 303/JMA-DA 5000 spectrometer; NMR spectra, JNM-GSX 400 (^{1}H-NMR, 400 MHz; ^{13}C-NMR, 100 MHz), JNM-EX270 (^{1}H-NMR, 270 MHz; ^{13}C-NMR, 67.8 MHz), JEOL JNM- PMX 60$_{SI}$ spectrometer with tetramethylsilane (TMS) as an internal standard; elemental analyses, Perkin-Elmer 2400 CHN Elemental Analyzer. The following experimental conditions were used for chromatography; column chromatography, Merck Kieselgel silica gel 60 (230—400 mesh); TLC, pre-coated TLC plates with 60F$_{254}$ (2 mm, Merck).

Synthesis of 2 An ethanol solution (20 ml) of KOH (0.59 g, 10.5 mmol), isoquinolone (1.45 g, 10 mmol), and benzyl chloride (1.35 g, 10.5 mmol) was heated at 100 °C for 10 h in a sealed tube. After removing the solvent *in vacuo*, the residue was washed with hexane and was recrystallized from isopropyl ether to afford **2** as colorless needles (2.33 g, 99%): mp 70 °C (isopropyl ether). IR ($CHCl_3$) cm^{-1}: 1650, 1599, 741, 692. ^{1}H-NMR ($CDCl_3$) δ: 5.22 (2H, s, CH_2), 6.47 (1H, d, J=7.4 Hz, H-4), 7.08 (1H, d, J=7.4 Hz, H-3), 7.24—7.39 (5H, m, H–Ph), 7.46—7.65 (3H, br m, H-5, 6, 7), 8.46 (1H, dd, J=1.2, 7.2 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 51.65, 106.38, 125.89, 126.32, 126.87, 127.79 (C2), 127.94, 128.06, 128.78 (C2), 131.27, 132.19, 136.90, 136.97, 162.24. MS *m/z*: 235 (M^+). High resolution (HR)-MS *m/z*: Calcd for $C_{16}H_{13}NO$, 235.0997. Found: 235.0985.

Synthesis of 4 A solution of **2** (0.47 g, 2 mmol) and phosphorus pentasulfide (0.467 g, 2.1 mmol) in pyridine (6 ml) was heated at 150 °C for 5 h. The reaction mixture was mixed with water (10 ml) and the resulting solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated. The residue was recrystallized from isopropyl ether to afford **4** as colorless needles (0.49 g, 97%): mp 95—97 °C. IR ($CHCl_3$) cm^{-1}: 1547, 1290, 773, 694. ^{1}H-NMR ($CDCl_3$) δ: 6.01 (2H, s, CH_2), 6.87 (1H, d, J=7.1 Hz, H-4), 7.31—7.34 (5H, m, H–Ph), 7.40 (1H, d, J=7.1 Hz, H-3), 7.54—7.61 (2H, br m, H-5, 7), 7.67 (1H, ddd, J=1.5, 7.5, 7.5 Hz, 6-H), 9.16 (1H, dd, J=1.5, 7.5 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 59.26, 112.42, 126.67, 127.94 (C3), 127.97, 128.55, 128.85 (C2), 132.11, 132.41, 133.05 (C2), 135.76, 184.63. MS *m/z*: 251 (M^+). HR-MS *m/z*: Calcd for $C_{16}H_{13}NS$, 251.0769. Found: 251.0727.

General Procedure for Synthesis of 2-Alkyl-1-alkylthioisoquinolinium Iodides (6a—c, 7) A solution of **4** (0.5 g, 2 mmol), **5a** (1.42 g, 10 mmol), and benzene (7 ml) was gently refluxed for 17 h. The resulting yellow precipitate was collected by filtration and was recrystallized from methanol to give **7** (0.6 g, 77%). Reactions of **3** with **5a**—**c** were carried out under similar conditions to afford **6a**, 1-ethylthio-(**6b**), and 1-isopropylthio-2-methylisoquinolinium iodide (**6c**). Yields are listed in Chart 2.

6a[9]: Yellow needles (methanol), mp 132—134 °C (mp 143—146 °C).[9] ^{1}H-NMR (DMSO-d_6) δ: 2.83 (3H, s, SMe), 4.66 (3H, s, NMe), 8.0—8.39 (3H, m, H-5, 6, 7), 8.75 (1H, d, J=7.0 Hz, H-4), 8.85 (1H, dd, J=2.0, 6.0 Hz, H-8), 9.0 (1H, d, J=7.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 20.10, 48.77, 125.08, 128.17, 129.71, 130.10, 131.85, 136.00, 136.90, 138.22, 160.87.

6b: Yellow needles (methanol), mp 104 °C. IR ($CHCl_3$) cm^{-1}: 1604, 773, 755. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (3H, dd, J=7.0, 7.0 Hz, CMe), 3.40 (2H, ddd, J=7.0, 7.0, 7.0 Hz, CH_2), 4.96 (3H, s, NMe), 8.00—8.50 (3H, m, H-5, 6, 7), 8.54 (1H, d, J=7.0 Hz, H-4), 8.87 (1H, br m, H-8), 9.21 (1H, d, J=7.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 15.08, 32.64, 48.90, 125.30, 128.13, 129.92, 130.85, 131.91, 136.09, 136.94, 138.48, 159.29. *Anal.* Calcd for $C_{12}H_{14}INS$: C, 43.52; H, 4.26; N, 4.23. Found: C, 43.33; H, 4.20; N, 4.03.

6c: Yellow needles (methanol), mp 139—140 °C. IR ($CHCl_3$) cm^{-1}: 1620, 785, 757. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (6H, d, J=7.0 Hz, CMex2), 3.91 (1H, m, J=7.0 Hz, CH), 4.76 (3H, s, NMe), 8.00—8.63 (3H, m, H-5, 6, 7), 8.73 (1H, d, J=7.0 Hz, H-4), 9.00 (1H, br m, H-8), 9.09 (1H, d, J=7.0 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 23.43 (C2), 44.83, 48.96, 125.57, 128.12, 130.08, 131.33, 132.02, 136.20, 137.06, 138.72, 158.20. *Anal.* Calcd for $C_{13}H_{16}INS$: C, 45.23; H, 4.67; N, 4.06. Found: C, 45.05; H, 4.37; N, 3.99.

7: Yellow needles (methanol), mp 110 °C. IR ($CHCl_3$) cm^{-1}: 1618, 725, 696. ^{1}H-NMR (CF_3COOD) δ: 2.67 (3H, s, SMe), 6.40 (2H, s, CH_2), 7.32—7.45 (5H, m, H–Ph), 8.17 (1H, ddd, J=1.3, 7.1, 8.4 Hz, H-6), 8.30 (1H, ddd, J=1.3, 7.1, 8.4 Hz, H-7), 8.45 (1H, dd, J=1.3, 8.4 Hz, H-5), 8.74 (1H, d, J=6.8 Hz, H-4), 8.87 (1H, dd, J=1.3, 8.4 Hz, H-8), 9.13 (1H, d, J=6.8 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: 21.62, 63.24, 111.90, 126.05, 127.51 (C2), 128.38, 128.46, 128.96 (C2), 132.19, 134.62, 136.50, 137.34, 137.33, 137.72, 161.43. *Anal.* Calcd for $C_{17}H_{16}INS$: C, 51.92; H, 4.10; N, 3.56. Found: C, 51.76; H, 3.83; N, 3.59.

General Procedure for Reaction of Isoquinolinium Salts (6a—c, 7) with Active Methylene Compounds (8a—h) To a suspension of NaH (15 mg, 0.6 mmol) in tetrahydrofuran (THF) (5 ml) was added dimethyl malonate (79 mg, 0.6 mmol) at 0 °C under N_2. The mixture was stirred for 10 min at room temperature followed by the addition of **6a** (165 mg, 0.5 mmol). The reaction mixture was stirred for 1.5 h at room temperature, then quenched with water (5 ml) followed by saturated $Na_2S_2O_3$ solution (3 ml). The reaction mixture was extracted with $CHCl_3$ and dried over $MgSO_4$. The organic layer was concentrated *in vacuo* to give 1,2-dihydro-1-[bis(methoxycarbonyl)methylene]-2-methylisoquinoline [**9a** (166 mg, 97%)]. Reactions of 1-ethylthio-, 1-isopropylthio-2-methylisoquinoline (**6b**, **c**) and **7** with dimethyl malonate (**8a**), methyl cyanoacetate (**8b**), malononitrile (**8c**), methyl acetoacetate (**8d**), acetylacetone (**8e**), ethyl benzoacetate (**8f**), 1,3-dioxocyclohexane (**8g**), and 1,3-dioxocyclopentane (**8h**) were carried out under the conditions shown in Table 1 and were similarly treated to give 1-[cyano(methoxycarbonyl)methylene]-1,2-dihydro-2-methyl-isoquinoline (**9b**), 1-[bis(cyano)methylene]-1,2-dihydro-2-methylisoquinoline (**9c**), 1-[acetyl(methoxy-carbonyl)methylene]-1,2-dihydro-2-methylisoquinoline (**9d**), 1-[bis(acetyl)methylene]-1,2-dihydro-2-methylisoquinoline (**9e**), 1-[benzoyl(ethoxycarbonyl)methylene]-1,2-dihydro-2-methylisoquinoline (**9f**), 1,2-dihydro-2-methyl-1-(2,6-dioxocyclohexylidene)isoquinoline (**9g**), 1,2-dihydro-2-methyl-1-(2,5-dioxocyclopentylidene)isoquinoline (**9h**), 2-benzyl-1,2-dihydro-1-[bis(methoxycarbonyl)methylene]isoquinoline (**10a**), 2-benzyl-1,2-dihydro-1-[cyano(methoxycarbonyl)methylene]isoquinoline (**10b**), 2-benzyl-1,2-dihydro-1-[bis(cyano)methylene]isoquinoline (**10c**), 1-[acetyl-(methoxycarbonyl)methylene]-2-benzyl-1,2-dihydroisoquinoline (**10d**), and 1-[bis(acetyl)methylene]-2-benzyl-1,2-dihydroisoquinoline (**10e**). Yields are listed in Table 1.

9a: Yellow crystalline powder (acetone), mp 237—239 °C. IR (KBr) cm^{-1}: 1720, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (6H, s, OMe×2), 4.22 (3H, s, NMe), 7.66 (1H, d, J=7.0 Hz, H-4), 7.72 (1H, d, J=2.0, 6.0, 8.0 Hz, H-7), 7.84—7.87 (2H, m, H-5, 6), 7.90 (1H, d, J=7.0 Hz, H-3), 8.50 (1H, dd, J=1.5, 8.0 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 45.00, 50.23 (C2), 121.07, 126.63, 129.69, 130.55, 131.40, 132.16, 133.54, 134.21, 136.31, 165.63, 167.27 (C2). MS *m/z*: 273 (M^+). *Anal.* Calcd for $C_{15}H_{15}N0_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.56; H, 5.07; N, 5.60.

9b: Yellow needles (benzene), mp 194—196 °C. IR (KBr) cm^{-1}: 2200, 1660. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, OMe), 4.06 (3H, s, NMe), 7.39 (1H, d, J=7.1 Hz, H-4), 7.65 (1H, d, J=7.1 Hz, H-3), 7.70—7.86 (3H, m, H-5, 6, 7), 8.93 (1H, dd, J=1.0, 7.8 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 47.22, 51.32, 118.61, 123.94, 126.97, 128.28, 129.33, 130.67, 133.96, 133.99, 135.59 (C2), 159.57, 167.77. MS *m/z*: 240 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_20_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.77; H, 4.94; N, 11.65.

9c: Yellow needles (acetone–chloroform), mp 226—227 °C. IR (KBr) cm^{-1}: 2200, 1630. ^{1}H-NMR (CF_3COOD) δ: 4.11 (3H, s, NMe), 7.10 (1H, d, J=7.3 Hz, H-4), 7.32 (1H, d, J=7.3 Hz, H-3), 7.65—7.84 (3H, m, H-5, 6, 7), 9.12 (1H, dd, J=1.0, 8.1 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 47.51, 116.00, 120.04 (C2), 125.91, 127.16, 128.53, 129.09, 133.89 (C2), 134.80 (C2), 158.17. MS: *m/z*: 207 (M^+). *Anal.* Calcd for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.28; H, 4.56; N, 20.31.

9d: Yellow crystalline powder (acetone), mp 224—225 °C. IR (KBr) cm^{-1}: 1660, 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s, COMe), 3.44 (3H, s, NMe), 4.22 (3H, s, OMe), 7.69—7.78 (1H, br m, H-aromatic), 7.71 (1H, d, J=7.3 Hz, H-4), 7.84—7.92 (2H, m, H-aromatic), 7.95 (1H, d, J=7.3 Hz, H-3), 8.45 (1H, dd, J=1.0, 8.6 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 28.44, 45.83, 49.74, 118.55, 121.85, 126.66, 129.90, 131.00, 131.93, 133.65, 134.49, 136.47, 167.00, 167.66, 190.04. MS *m/z*: 257 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.90; H, 5.97; N, 5.50.

9e: Yellow crystalline powder (acetone), mp 210—211 °C. IR (KBr) cm^{-1}: 1670, 1640. ^{1}H-NMR (CF_3COOD) δ: 1.95 (6H, s, COMe×2), 4.54 (3H, s, NMe), 8.20 (1H, dd, J=7.6, 7.6 Hz, H-6 or 7), 8.34—8.39 (3H, m, H-aromatic), 8.51 (1H, d, J=6.8 Hz, H-3 or 4), 8.67 (1H, d, J=6.8 Hz, H-3 or 4). ^{13}C-NMR (CF_3COOD) δ: 25.54 (C2), 48.81, 107.62, 130.12, 130.67, 131.18, 132.31, 136.36, 139.08, 140.78, 141.72, 157.94, 196.13 (C2). MS *m/z*: 241 (M^+). HR-MS *m/z*: Calcd for $C_{15}H_{15}NO_2$, 241.1109. Found: 241.1111.

9f: Yellow crystalline powder (benzene), mp 175—178 °C. IR (KBr) cm^{-1}: 1640, 1620. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, dd, J=8.0, 8.0 Hz, CMe), 3.38 (2H, ddd, J=8.0, 8.0, 8.0 Hz, $COOCH_2$), 4.16 (3H, s, NMe), 7.16—8.85 (10H, m, H-3, 4, 5, 6, 7, Ph), 8.32—8.60 (1H, m, H-8). ^{13}C-NMR ($CDCl_3$) δ: 14.06, 45.93, 58.52, 91.11, 121.18, 126.73, 127.40 (C2), 127.45 (C2), 128.54, 129.71, 130.81, 131.81, 133.79, 134.21, 136.34, 144.35, 166.04, 168.12, 188.91. MS *m/z*: : 333 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.74; N, 4.20. Found: C, 75.61; H, 6.00; N, 4.17.

9g: Pale yellow crystalline powder (benzene), mp 230—233 °C. IR (KBr) cm^{-1}: 1620, 1600, 820, 750. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.40 (2H, m, CH_2),

2.66—2.79 (4H, m, $COCH_2$×2), 4.23 (3H, s, NMe), 7.73 (1H, d, J=7.0 Hz, H-4), 7.72—8.00 (3H, m, H-5, 6, 7), 7.96 (1H, d, J=7.0 Hz, H-3), 8.43 (1H, br m, H-8). ^{13}C-NMR ($CDCl_3$) δ: 21.52, 37.13 (C2), 46.09, 105.84, 122.62, 126.76, 129.89, 130.15, 132.35, 133.97, 134.95, 136.47, 165.31, 192.17 (C2). MS *m/z*: 253 (M^+). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.44; H, 6.02; N, 5.44.

9h: Yellow needles (benzene), mp 291—293 °C. IR (KBr) cm^{-1}: 1625, 1600, 810, 755. ^{1}H-NMR ($CDCl_3$) δ: 2.73 (4H, s, $COCH_2$×2), 4.33 (3H, s, NMe), 7.50—8.06 (5H, m, H-3, 4, 5, 6, 7), 8.43 (1H, m, H-8). ^{13}C-NMR ($CDCl_3$) δ: 34.48 (C2), 46.83, 106.45, 121.69, 126.68, 128.46, 129.82, 132.66, 134.21, 135.02, 136.31, 159.89, 199.66 (C2). MS *m/z*: 239 (M^+). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.87. Found: C, 75.03; H, 5.34; N, 5.87.

10a: Red plates (acetone), mp 239 °C. IR (KBr) cm^{-1}: 1701, 1595, 758. ^{1}H-NMR ($CDCl_3$) δ: 3.63 (6H, s, OMe×2), 5.76 (2H, s, CH_2), 7.25 (2H, dd, J=2.0, 6.6 Hz, H–Ph), 7.32—7.39 (3H, m, H–Ph), 7.58 (1H, d, J=7.0 Hz, H-4), 7.72—7.88 (4H, m, H-3, 5, 6, 7), 8.60 (1H, d, J=8.2 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 50.10 (C2), 60.49, 121.38, 126.63 (C2), 128.95, 129.04, 129.30 (C3), 129.81, 131.34, 132.26, 132.69, 134.54 (C2), 134.90, 136.33, 166.25, 167.24. MS *m/z*: 349 (M^+), 230. HR-MS *m/z*: Calcd for $C_{21}H_{19}NO_4$, 349.1314. Found: 349.1283.

10b: Red needles (acetone), mp 91—93 °C. IR (KBr) cm^{-1}: 2172, 1713, 1643, 756. ^{1}H-NMR ($CDCl_3$) δ: 3.81 (3H, s, OMe), 5.77 (2H, s, CH_2), 7.17—7.24 (2H, m, H–Ph), 7.34—7.39 (4H, m, H-4, Ph), 7.50 (1H, d, J=7.2 Hz, H-3), 7.70—7.87 (3H, m, H-5, 6, 7), 9.09 (1H, d, J=8.9 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 51.29, 61.92, 118.47, 124.12, 127.02 (C2), 128.28, 128.50, 129.11 (C2), 129.42 (C2), 130.66, 132.56, 134.16, 135.08, 135.31 (C2), 139.87, 168.09. MS *m/z*: : 316 (M^+), 285, 257, 91. HR-MS *m/z*: Calcd for $C_{20}H_{16}N_20_2$, 316.1212. Found: 316.1248.

10c: Yellow needles (acetone), mp 215—216 °C. IR (KBr) cm^{-1}: 2191, 2162, 1629, 732. ^{1}H-NMR ($CDCl_3$) δ: 5.62 (2H, s, CH_2), 7.00 (1H, d, J=7.0 Hz, H-4), 7,18—7.26 (3H, m, H-3, Ph), 7.38—7.44 (3H, m, H–Ph), 7.65—7.72 (2H, m, H-5, 6), 7.80 (1H, dd, J=1.0, 7.6 Hz, H-7), 9.13 (1H, d, J=8.6 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 61.42, 115.60, 119.98, 126.15, 127.13, 128.36, 128.53, 128.97, 129.11, 129.42, 132.83 (C5), 133.89, 134.00, 134.63, 158.54. MS: *m/z*: 283 (M^+). *Anal.* Calcd for C, 80.54; N, 14.83; H, 4.63. Found: C, 80.61; N, 14.75; H, 4.91.

10d: Yellow plates (acetone), mp 250 °C. IR (KBr) cm^{-1}: 1733, 1716, 1655, 772. ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s, COMe), 3.43 (3H, s, OMe), 5.55 (1H, d, J=15.0 Hz, CH–Ph), 5.94 (1H, d, J=15.0 Hz, CH–Ph), 7.25 (5H, s, H–Ph), 7.66 (1H, d, J=7.1 Hz, H-4), 7.72—7.92 (4H, m, H-3, 5, 6, 7), 8.53 (1H, d, J=8.4 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 28.37, 49.65, 60.52, 122.06, 126.72, 128.92 (C2), 129.11 (C2), 129.31, 130.02, 130.84 (C2), 132.42, 134.02 (C2), 130.84, 136.56 (C2), 167.60, 190.13. MS *m/z*: 333 (M^+), 274, 260, 91. HR-MS *m/z*: Calcd for $C_{21}H_{19}NO_3$, 333.1365. Found: 333.1378.

10e: Yellow plates (acetone), mp 190 °C. IR ($CHCl_3$) cm^{-1}: 1735, 1718, 1699, 1629, 772, 686. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (6H, s, COMe×2), 5.74 (2H, s, CH_2), 7.30—7.35 (2H, m, H–Ph), 7.36—7.41 (3H, m, H–Ph), 7.71—7.82 (2H, m, H-aromatic), 7.86—7.94 (3H, m, H-aromatic), 8.57 (1H, d, J=8.6 Hz, H-8). ^{13}C-NMR ($CDCl_3$) δ: 29.65, 30.88, 60.42, 122.27, 126.84, 129.16 (C2), 129.43 (C3), 129.46, 132.28 (C2), 132.47, 134.17, 135.20, 136.70 (C2), 169.98, 196.22 (C2). MS *m/z*: 317 (M^+), 274, 260, 232. HR-MS *m/z*: Calcd for $C_{21}H_{19}NO_2$, 317.1416. Found: 317.1387.

General Procedure for Reaction of 10a, d, e with Acetic Anhydride A mixture of **10a** (0.349 g, 1.0 mmol) and acetic anhydride (4 ml) was refluxed for 4 h and concentrated *in vavuo.* The residue was dissolved in water (5 ml), and the resulting solution was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo.* The residue was purified using column chromatography on aluminum oxide ($CHCl_3$–acetone, 2 : 1) to give 2-acetoxy-1-methoxycarbonyl-3-phenylpyrrolo[2-1-*a*]isoquinoline [**11a** (0.357 g, 99%)]. Reactions of **10d, e** with acetic anhydride were similarly performed to give 2-acetoxy-1-acetyl-3-phenylpyrrolo[2-1-*a*]isoquinoline (**11b**), and 1-acetyl-2-methyl-3-phenylpyrrolo[2-1-*a*]isoquinoline (**11c**). Yields are listed in Chart 3.

11a: Yellow needles (Et_2O), mp 165—166 °C. IR ($CHCl_3$) cm^{-1}: 1764, 1702, 1606. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, COMe), 3.95 (3H, s, COOMe), 6.93 (1H, d, J=7.4 Hz, H-6), 7.45—7.60 (8H, m, H-7, 8, 9, Ph), 7.83 (1H, d, J=7.4 Hz, H-5), 9.40 (1H, d, J=8.0 Hz, H-10). ^{13}C-NMR ($CDCl_3$) δ: 20.64, 51.60, 101.45, 113.71, 119.18, 121.32, 125.40, 126.63, 126.92, 127.62, 127.65, 127.81, 127.84, 128.83, 129.03, 129.15, 129.23, 129.81, 130.08, 137.31, 164.77, 170.01. MS: *m/z*: 359 (M^+), 317, 285, 228. HR-MS *m/z*: Calcd for $C_{22}H_{17}NO_4$, 359.1158. Found: 359.1187.

11b: Yellow plates (acetone), mp 145—146 °C. IR ($CHCl_3$) cm^{-1}: 1764, 1718, 1700, 1605. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s, COMe), 2.63 (3H, s, OCOMe), 6.95 (1H, dd, J=0.7, 7.3 Hz, H-6), 7.46—7.63 (8H, m, H-7, 8, 9, Ph), 7.80 (1H, d, J=7.3 Hz, H-5), 9.10 (1H, ddd, J=0.7, 1.4, 6.4 Hz, H-10). ^{13}C-NMR ($CDCl_3$) δ: 20.82, 31.10, 111.82, 114.10, 119.05, 121.16, 125.44, 126.18, 126.98, 127.59, 127.88, 127.91, 128.68, 128.94, 129.11, 129.23 (C2), 130.03 (C2), 136.88, 169.43, 194.95. MS: *m/z*: 343 (M^+), 301, 286. HR-MS *m/z*: Calcd for $C_{22}H_{17}NO_4$, 359.1158. Found: 359.1187.

11c: Colorless oil. IR ($CHCl_3$) cm^{-1}: 1718, 1655, 1604. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s, COMe), 2.71 (3H, s, Me), 6.78 (1H, dd, J=0.8, 7.3 Hz, H-6), 7.39—7.56 (8H, m, H-7, 8, 9, Ph), 7.68 (1H, d, J=7.3 Hz, H-5), 8.52 (1H, dd, J=0.8, 8.3 Hz, H-10). ^{13}C-NMR ($CDCl_3$) δ: 12.11, 32.39, 112.42, 119.74, 120.89, 121.77, 125.04, 125.26, 126.21, 126.90, 126.93, 127.35, 128.41, 128.69, 128.85, 129.04 (C2), 130.53, 130.94 (C2), 200.30. MS: *m/z*: 299 (M^+), 284. HR-MS *m/z*: Calcd for $C_{21}H_{17}NO$, 299.1310. Found: 299.1311.

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