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New method for the synthesis of pyrromethanes

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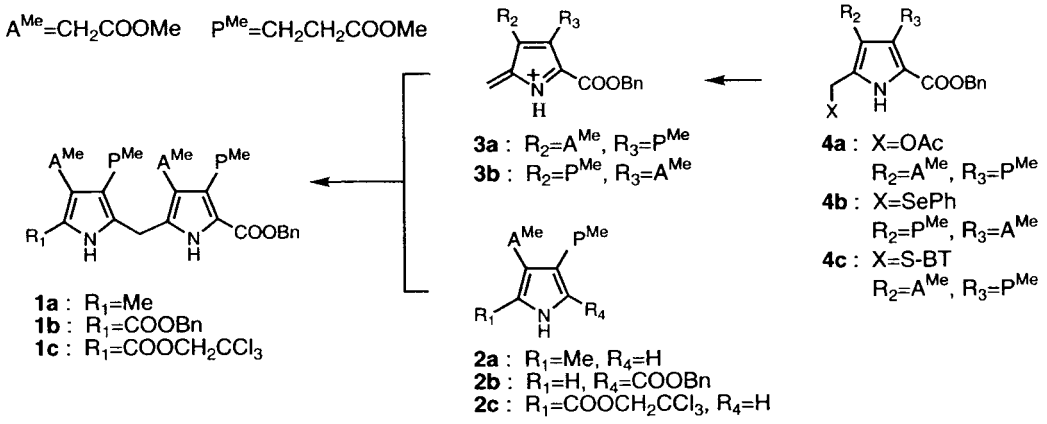
Abstract—Coupling reaction of 2-mercaptobenzothiazolylmethylpyrrole with α-free pyrrole in the presence of silver(I) triflate proceeds smoothly at room temperature to give a pyrromethane in excellent yield. The azafulvenium ion, an active form that reacts with α-free pyrrole, also reacts with pyrromethane rapidly under similar neutral conditions to afford an equilibrated mixture of pyrromethanes in good yield.

1. Introduction[1]

Pyrromethane **1a** is usually synthesized by coupling reaction of α-acetoxymethylpyrrole **4a** with α-free pyrrole **2a** in the presence of protonic acids (*p*-TsOH, TFA, AcOH) and Lewis acid ($SnCl_4$) as catalyst.[2] Montmorillonite clay has also been shown to be useful for the synthesis of pyrromethane[3] and bilane.[4] The azafulvenium ion **3a**, generated from **4a** under these conditions, is a key intermediate in the coupling reaction with **2a**. In 1991, Battersby et al. reported a new method for pyrromethane synthesis involving treatment of α-free pyrrole **2b** and phenylselenomethylpyrrole **4b** in dry degassed dichloromethane containing the benzene complex of copper(I) triflate in the presence of calcium carbonate. The coupling reaction was rapid and product **1b** was isolated after 5 min at −23°C in 91% yield.[5] In this reaction, **4b** eliminates the phenylseleno-group with the aid of the copper(I) catalyst to yield the required azafulvene intermediate **3b**, as shown in Scheme 1.

At this laboratory, attention has been directed to the chemistry of pyrromethane synthesis, particularly to develop a method for the effective synthesis of bilanes[4,6] and oligopyrroles[7] related to the biosynthetic mechanism of uroporphyrinogen III.[8] A few preliminary experiments to generate **3a** from **10** were made by using several activating reagents of hydroxy group as follows: treatment of **10** with carbonyldiimidazole or triphenylphosphine–CCl_4 in the presence of **2c** did not produce any pyrromethane, however, reaction of **10** with **2c** by the aid of diethylaminosulfur trifluoride (−78°C to rt, in CH_2Cl_2; 1.5 h) or 2-chloro-1-methylpyridinium iodide (refluxed with triethylamine in CH_3CN; 5 h), produced the desired pyrromethane **1c** in unsatisfied 55 or 64% yield, respectively. While continuing the synthesis of



Scheme 1.

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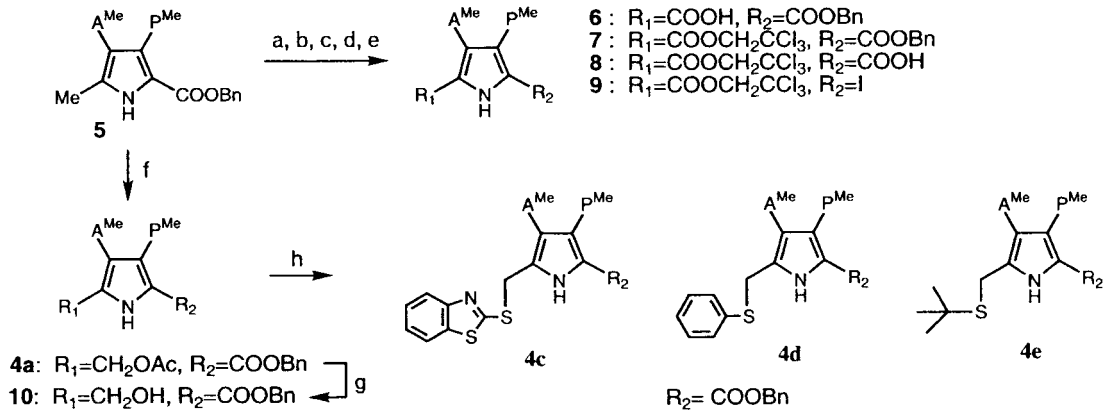


Scheme 2. Reagents: (a) SO_2Cl_2, then H_2O; (b) CCl_3CH_2OH/DCC-DMAP; (c) H_2/Pd–C; (d) I_2/KI, $NaHCO_3$; (e) H_2/Pd–C; (f) $Pb(OAc)_4$/AcOH; (g) 0.5N KOH–MeOH; (h) RSH/*p*-TsOH, CH_2Cl_2.

pyrromethanes under mild and neutral conditions, coupling reaction between α-free pyrrole **2c** and 2-mercaptobenzothiazolyl-(S-BT)-methylpyrrole derivative **4c** was found to proceed smoothly at room temperature using a thiophile reagent such as silver(I) triflate in excellent yield. This paper reports the detail results and experimental conditions for the coupling reaction of α-free pyrroles with 2-mercaptomethylpyrrole derivatives in the presence of thiophile reagents such as Ag(I) or Hg(II) salts, which may catalyze the formation of azafulvenium ion **3a** from **4c**, the same key intermediate, as shown in Scheme 1.

2. Results and discussions

Reactions of three different mercaptomethylpyrrole derivatives with three thiophile reagents were examined. Required substrates **2c** and **4c**–**4e** were prepared from the known benzyl 5-methylpyrrole-2-carboxylate **5**[9] in the conventional way as shown in Scheme 2.

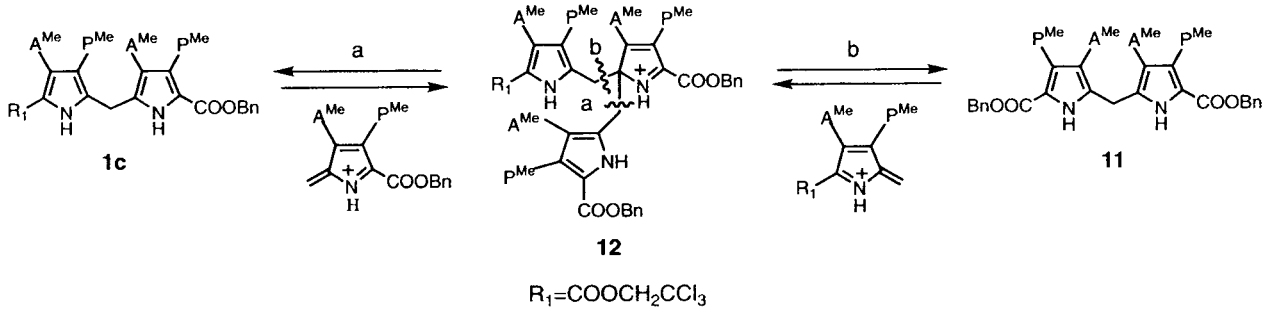
α-Free pyrrole **2c** was prepared from **5** by the method reported by Battersby as follows.[10] Treatment of **5** with SO_2Cl_2 in dichloromethane at 0°C followed by hydrolysis in boiling H_2O–acetone yielded 5-carboxylic acid pyrrole derivative **6** in 73% yield. Esterification of **6** with 2,2,2-trichloro-ethanol-DCC-DMAP produced trichloroethyl ester **7** (85%), which was then converted to 2-carboxylic acid pyrrole derivative **8** by the usual catalytic hydrogenolysis in 94% yield. Iodination of **8** with I_2/KI in a mixture of dichloromethane–H_2O–$NaHCO_3$ gave **9** (86%), and subsequent reductive deiodination (H_2/10% Pd–C in dichloromethane; 97%) yielded the desired α-free pyrrole **2c**. The other substrates, 2-mercaptomethylpyrrole derivatives **4c**–**4e** were prepared by treatment of α-acetoxymethylpyrrole **4a**, derived from **5** in the usual way ($Pb(OAc)_4$/AcOH, rt), with three mercapthanes, 2-mercaptobenzothiazole, thiophenol and *tert*-butylmercapthane in the presence of a catalytic amount of *p*-toluenesulfonic acid in dry dichloromethane for 16 h at room temperature in good yields.

A general procedure for coupling reaction between **2c** and **4c**–**4e** is as follows: a solution of mercaptomethylpyrrole **4c**–**4e** (0.10 mmol) and α-free pyrrole **2c** (0.12 mmol) in dry benzene (5 ml) was stirred with thiophile reagent (0.15 mmol) in the presence of Na_2HPO_4 (0.35 mmol) at room temperature. After dilution with benzene, the mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give pyrromethane **1c**. Yields of pyrromethane as determined from the amounts **4c**–**4e** under the various conditions are summarized in Table 1. 2-Mercaptobenzothiazolylmethylpyrrole **4c** was clearly found to be the most promising substrate, compared with phenylmercaptomethyl- and *tert*-butylmercaptomethylpyrrole derivatives and the most efficient thiophile reagent was CF_3SO_3Ag compared to other reagents such as CF_3COOAg and $(CF_3COO)_2Hg$. As shown in entry 4, coupling reaction of **2c** with **4c** with the aid of CF_3SO_3Ag proceeded quite rapidly (10 min) and yield of the desired pyrromethane was excellent (98%).

It is of interest to note that reaction of excess **4c** (1.2 equiv.) with **2c** (1 equiv.), in contrast to the amount of substrates under similar conditions, gave *symmetric* pyrromethane **11** (10% yield) as a minor product along with the desired pyrromethane **1c**. Cross coupling reaction **1c** with azafulvenium ion **3a** may generate bis-(pyrrolylmethyl)pyrrolenine intermediate **12**, followed by cleavage of C–C bond to yield **11** or **1c**. As shown in Scheme 3, symmetrical pyrromethane **11** should be produced by rapid equilibration through intermediate **12**. When pyrromethane **1c** (10 mg, 13 μmol)

Table 1. Synthesis of pyrromethane **1c** by coupling reaction of mercaptomethylpyrrole derivatives **4c**–**4e** with α-free pyrrole derivative **2c**

Entry	Reagent	Substrate	Time	Yield of **1c** (%)
1	CF_3COOAg	**4c**	1 h	67
2		**4d**	6 h	60
3		**4e**	12 h	51
4	CF_3SO_3Ag	**4c**	10 min	98
5		**4d**	6 h	83
6		**4e**	12 h	58
7	$(CF_3COO)_2Hg$	**4c**	6 h	10
8		**4d**	6 h	23
9		**4e**	6 h	49



Scheme 3.

was reacted with four equiv. of **4c** (28 mg, 52 μmol) under similar conditions, **11** (7.5 mg) was obtained as the major product in addition to recovered **1c** (2.0 mg) from the reaction mixture. Application of this method to the synthesis of oligopyrrole derivative is now being studied.[11]

3. Experimental

3.1. General

Melting points were not corrected. IR spectra were determined on JASCO IR-810 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-GX 270 or JNM-GX 400 spectrometer. The chemical shifts (δ) are given relative to TMS (δ: 0.00) or $CDCl_3$ (δ_H: 7.26 and δ_C: 77.03) as internal standard and coupling constants (J) in Hz. Mass spectra were obtained with a Hitachi M-80 (EI) or JEOL HX-110 (FAB) spectrometers. Column chromatography was performed on Kanto Chemical silica gel (over 100 mesh) or Wakogel C-300 (flash column chromatography). TLC was carried out on Kieselgel $60F_{254}$ plates (Art. 5744, Merck). Unless otherwise noted, all reaction mixtures were dried after work up over anhydrous Na_2SO_4.

3.1.1. 5-Benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylic acid (6). To a solution of benzyl 3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-methylpyrrole-2-carboxylate **5** (5.0 g, 13.40 mmol) in CH_2Cl_2 (50 ml) was added sulfuryl chloride (3.4 ml, 42.32 mmol) dropwise at 0°C. After being stirred for 2 h at room temperature, the mixture was added slowly to a mixture of boiling acetone–water (2:1 v/v; 200 ml) and allowed to stand at the same temperature for 15 min. After cooling, the acetone was evaporated under reduced pressure and the product was extracted with CH_2Cl_2 (50 ml×3). The combined extracts were evaporated and the residue was dissolved in ether (200 ml) and then the carboxylic acid was transferred into 10% aqueous $NaHCO_3$ solution (75 ml×3). After the combined aqueous solution had been washed with ether (50 ml), it was carefully acidified with conc. HCl at 0°C, and the liberated carboxylic acid was extracted with CH_2Cl_2 (50 ml×3). The combined organic phase was washed with brine, dried and then concentrated to dryness. The residue was re-precipated from MeOH–H_2O to give **6** (3.94 g, 73.0% yield) as an amorphous solid. EIMS *m/z*: 403 (M^+), 402, 373, 341, 314, 282; IR(KBr): 3250 (br), 1730, 1710, 1560, 1438, 1345, 1270, 1168, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52 (2H, t, J=7.4 Hz), 2.99 (2H, t, J=7.4 Hz), 3.61 (3H, s), 3.67 (3H, s), 3.89 (2H, s), 5.33 (2H, s), 7.38–7.40 (5H, m), 9.67 (1H, brs); ^{13}C NMR: 20.15, 30.04, 34.60, 51.55, 52.15, 66.77, 121.54, 122.38, 124.02, 128.47, 128.56, 128.65, 130.41, 135.41, 160.21, 164.93, 172.61, 173.38.

3.1.2. 2,2,2-Trichloroethyl 5-benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylate (7). To a solution of **6** (3.5 g, 8.68 mmol) and 2,2,2-tri-chloroethanol (4.16 ml, 43.4 mmol) in CH_2Cl_2 (125 ml) were added *N*,*N*′-dicyclohexylcarbodiimide (3.58 g, 17.35 mmol) and 4-dimethylaminopyridine (0.53 g, 4.38 mmol) and the mixture was stirred at room temperature for 15 h. After dilution with ether (125 ml), the mixture was filtered through celite column. The filtrate and washings (ether, 20 ml) of the column were combined and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt=5:1) to give **7** (3.94 g; 85.0% yield). Mp 92–94°C (crystallized from MeOH–hexane); IR (KBr): 3300, 1730, 1710, 1665, 1438, 1375, 1343, 1275, 1125 cm^{-1}; EIMS *m/z*: 535 and 533 (M^+), 501, 410, 382; ^{1}H NMR ($CDCl_3$) δ: 2.53 (2H, t, J=7.4 Hz), 3.00 (2H, t, J=7.4 Hz), 3.62 (3H, s), 3.67 (3H, s), 3.94 (2H, s), 4.92 (2H, s), 5.35 (2H, s), 7.36–7.40 (5H, m), 9.70 (1H, brs); ^{13}C NMR: 20.04, 30.01, 34.45, 51.58, 52.09, 66.99, 74.15, 94.60, 121.16, 123.00, 124.45, 128.59, 128.65, 128.75, 130.89, 135.20, 158.57, 159.83, 171.26, 173.23; Anal. Calcd for $C_{22}H_{22}NO_8Cl_3$: C, 49.41; H, 4.15; N, 2.62%. Found: C, 49.34; H, 4.24; N, 2.69%.

3.1.3. 3-(2-Methoxycarbonylethyl)-4-methoxycarbonylmethyl-5-(2,2,2-trichloroethoxycarbonyl) pyrrole-2-carboxylic acid (8). To a solution of **7** (3.5 g, 6.54 mmol) in MeOH (50 ml) was added 10% Pd–C (3.5 g) and the mixture was stirred vigorously at 35°C for 4 h under hydrogen atmosphere. After filtration of the reaction mixture through celite and washing of the column with MeOH, the combined MeOH solution was evaporated under reduced pressure. The residue was crystallized from MeOH–hexane to give **8** (2.75 g, 94.5% yield). Mp 143–145°C; IR (KBr): 3250 (br), 1730, 1715, 1665, 1438. 1372, 1343, 1260, 1205, 1175, 1130 cm^{-1}; EIMS *m/z*: 445 and 443 (M^+), 411, 383, 309, 281, 249, 222; ^{1}H NMR ($CDCl_3$) δ: 2.63 (2H, t, J=7.4 Hz), 3.06 (2H, t, J=7.4 Hz), 3.67 (3H, s), 3.70 (3H, s), 3.98 (2H, s), 4.95 (2H, s), 9.82 (1H, br s); ^{13}C NMR: 19.96, 30.04, 34.34, 51.74, 52.20, 74.20, 94.53, 122.01, 122.40, 124.59, 132.17, 158.55, 164.31, 171.41, 173.55; Anal. Calcd for $C_{15}H_{16}NO_8Cl_{13}$: C, 40.52; H, 3.63; N, 3.15%. Found: C, 40.89; H, 3.77; N, 3.17%.

3.1.4. 2,2,2-Trichloroethyl 5-iodo-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylate (9). To a solution of the foregoing carboxylic acid **8** (2.62 g, 5.89 mmol) in the mixture of CH_2Cl_2 (30 ml) and H_2O (20 ml) was added $NaHCO_3$ powder (1.5 g) under vigorous stirring at 50°C. The aqueous solution (10 ml) of I_2 (1.73 g, 6.81 mmol) and KI (1.76 g, 10.60 mmol) was added to the above mixture at 50°C during 5 min. Refluxing was continued with vigorous stirring, for further 25 min and then the mixture was cooled. After addition of aqueous solution of $NaHSO_3$ to destroy the excess of iodine, the reaction mixture was extracted with CH_2Cl_2 (30 ml×3). The combined organic phase was washed with brine, dried and concentrated. The residual solid was purified by flash column chromatography on silica gel (hexane–AcOEt=6:1) to give the iodopyrrole **9** which was crystallized from CH_2Cl_2-hexane (2.67 g, 86.0% yield). Mp 134–136°C; IR (KBr): 3270, 1730, 1710, 1560, 1410, 1340, 1230, 1175, 1120 cm^{-1}; EIMS *m/z*: 527 (M^+), 496, 468, 400, 350, 250; ^1H NMR ($CDCl_3$) δ: 2.49 (2H, t, *J*=7.4 Hz), 2.72 (2H, t, *J*=7.4 Hz), 3.68 (3H, s), 3.69 (3H, s), 3.95 (2H, s), 4.90 (2H, s), 9.20 (1H, brs); ^{13}C NMR; 21.79, 30.71, 31.12, 51.74, 52.10, 73.94, 94.85, 123.19, 124.20, 124.23, 129.69, 158.12, 171.28, 173.03; Anal. calcd for $C_{14}H_{15}NO_6Cl_3I$: C, 31.94; H, 2.87; N, 2.66%. Found: C, 31.67; H, 2.87, N, 2.63%.

3.1.5. 2,2,2-Trichloroethyl 4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole-2-carboxylate (2c). A solution of iodo pyrrole **9** (1.21 g, 2.30 mol) in MeOH (12 ml) was vigorously stirred with 10% Pd–C (0.12 g) and NaOAc (0.69 g) under hydrogen atmosphere until the uptake of gas ceased. The catalyst was removed by filtration through celite and the filtrate was evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (80 ml) and 5% aqueous Na_2CO_3 solution (20 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to give an amorphous solid which was crystallized from the mixture of CH_2Cl_2-hexane, giving colorless prisms of **2c** (0.895 g, 97.0% yield). Mp: 94–95°C; IR (KBr): 3340, 1735, 1710, 1573, 1510, 1418, 1410, 1340, 1273, 1170, 1115 cm^{-1}; EIMS *m/z*: 401 and 399 (M^+), 367, 341, 307, 268, 224; ^1H NMR ($CDCl_3$) δ: 2.49 (2H, t, *J*=7.4 Hz), 2.69 (2H, t, *J*=7.4 Hz), 3.60 (3H, s), 3.61 (3H, s), 3.86 (2H, s), 4.82 (2H, s), 6.77 (1H, brs), 9.02 (1H, brs); ^{13}C NMR: 20.11, 30.30, 34.68, 51.68, 52.02, 73.79, 95.08, 118.62, 121.66, 123.65, 124.97, 158.94, 171.60, 173.36; Anal. Calcd for $C_{14}H_{16}NO_6Cl_3$: C, 41.97; H, 4.03; N, 3.50%. Found: C, 41. 86; H, 4.05; N, 3.52%.

3.1.6. Benzyl 5-acetoxymethyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (4a). α-Methylpyrrole derivative **5** (2.25 g, 6.03 mmol) was stirred at rt for 16 h with lead tetraacetate (3.24 g, 7.31 mmol) in AcOH (180 ml) under nitrogen atmosphere. The residue, obtained from evaporation of the solvent, was partitioned between CH_2Cl_2 (200 ml) and saturated aq. $NaHCO_3$ (100 ml) and the aqueous layer was extracted with fresh CH_2Cl_2 (50 ml×3). The combined CH_2Cl_2 extracts were dried and concentrated to dryness. The residue was crystallized from CH_2Cl_2–hexane to give **4a** (2.38 g, 91.7% yield); Mp 106–108°C; IR (KBr) 3295, 1740, 1670, 1472, 1438, 1370, 1350, 1287, 1240, 1188 cm^{-1}; EIMS *m/z*: 431 (M^+), 400, 372, 340, 280, 266; ^1H NMR ($CDCl_3$): δ: 2.01 (3H, s), 2.51 (2H, t, *J*=7.4 Hz), 3.01 (2H, t, *J*=7.4 Hz), 3.51 (2H, s), 3.57 (3H, s), 3.63 (3H, s), 5.02 (2H, s), 5.26 (2H, s), 7.30–7.34 (5H, m), 9.35 (1H, brs); ^{13}C NMR: 20.40, 20.84, 29.38, 34.66, 51.48, 52.12, 56.85, 66.18, 116.96, 119.12, 128.33, 128.41, 128.62, 128.79, 129.99, 135.89, 160.42, 171.43, 171.85, 173.54; Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.24; H, 5.80; N, 3.25%. Found: C, 61.49; H, 5.74; N, 3.41%.

3.1.7. Benzyl 5-(2-mercaptobenzothiazolylmethyl)-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (4c). To a solution of 2-acetoxymethylpyrrole **10** (2.0 g, 4.64 mmol) and *p*-TsOH (0.080 g, 0.42 mmol) in CH_2Cl_2 (100 ml) was added 2-mercaptobenzothiazole (1.16 g, 6.95 mmol) under nitrogen atmosphere and stirred at room temperature for 16 h in the dark. After dilution with CH_2Cl_2 (50 ml), the mixture was washed with saturated aq. solution of $NaHCO_3$, brine, dried and then concentrated to dryness. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt=3:1) to give **4c** (2.40 g, 96.1% yield): mp 93–95°C (crystallized from MeOH); IR (KBr) 3300, 1735, 1700, 1575, 1503, 1458, 1427, 1260, 1170 cm^{-1}; EIMS *m/z*: 538 (M^+), 372, 298, 167, 91; ^1H NMR ($CDCl_3$) δ: 2.56 (2H, t, *J*=7.4 Hz), 3.04 (2H, t, *J*=7.4 Hz), 3.54 (2H, s), 3.62 (3H, s), 3.69 (3H, s), 4.49 (2H s), 5.25 (2H, s), 7.30–7.34 (7H, m), 7.64–7.75 (2H, m), 10.92 (1H, brs); ^{13}C NMR: 20.39, 27.87, 29.68, 34.72, 51.45, 52.19, 65.89, 115.05, 118.42, 121.03, 121.31, 124.56, 126.44, 128.23, 128.43, 128.58, 130.12, 130.72, 135.39, 136.08, 152.48, 160.27, 167.83, 171.90, 173.65; Anal. Calcd for $C_{27}H_{26}N_2O_6S_2$: C, 60.21; H, 4.87; N, 5.20%. Found: C, 60.10; H, 4.88; N, 5.20%.

In the same way, **4d** and **4e** were synthesized in high yield, respectively.

4d. Mp 95–97°C (crystallized from MeOH), IR (KBr): 3350, 1738, 1700, 1580, 1455, 1437, 1267, 1168 cm^{-1}; EIMS *m/z*: 481 (M^+), 422, 372, 298; ^1H NMR ($CDCl_3$) δ: 2.51 (2H, t, *J*=7.4 Hz), 2.99 (2H, t, *J*=7.4 Hz), 3.37 (2H, s), 3.61 (3H, s), 3.63 (3H, s), 4.05 (2H, s), 5.26 (2H, s), 7.22–7.27 (5H, m), 7.34–7.39 (5H, m), 8.89 (1H, brs); ^{13}C NMR: 20.48, 29.36, 30.37, 34.70, 51.46, 52.06, 66.03, 115.44, 117.99, 127.39, 128.29, 128.39, 128.60, 129.13, 130.42, 130.63, 131.04, 134.71, 135.98, 160.30, 171.83, 173.54; Anal. Calcd for $C_{26}H_{27}NO_6S$; C, 64.85; H, 5.65; N, 2.91%. Found C, 64.64; H, 5.68; N, 2.96%.

4e. Mp 87–88°C (crystallized from MeOH), IR (KBr): 3300, 1735, 1700, 1580, 1500, 1455, 1438, 1365, 1267, 1168 cm^{-1}; EIMS *m/z*: 461 (M^+), 404, 372, 344, 314, 282; ^1H NMR ($CDCl_3$) δ: 1.30 (9H, s), 2.52 (2H, t, *J*=7.4 Hz), 3.00 (2H, t, *J*=7.4 Hz), 3.50 (2H, s), 3.61 (3H, s), 3.67 (3H, s), 5.29 (2H, s), 7.32–7.40 (5H, m), 9.06 (1H, brs); ^{13}C NMR: 20.53, 65.95, 114.47, 117.52, 128.22, 128.34, 128.59, 130.88, 131.38, 136.12, 160.45, 171.95, 173.59; Anal. Calcd for $C_{24}H_{31}NO_6S$; C, 62.45; H, 6.77, N, 3.03%. Found: C, 62.31; H, 6.81; N, 3.03%.

3.1.8. Benzyl 5-hydroxymethyl-3-(2-methoxycarbonylethyl)-4-methoxycarbonylmethylpyrrole-2-carboxylate (10). A solution of **4a** (431 mg, 1.00 mmol) in degassed 0.5N KOH–MeOH (10 ml) was allowed to stand at 0°C

for 30 min. After dilution with AcOEt (100 ml), the mixture was washed with brine, dried and concentrated. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt=1:1) to give **10** (280 mg, 72% yield). Mp 116–118°C (crystallized from MeOH–hexane); IR (KBr): 3310, 1738, 1690, 1440, 1268, 1175, 1083 cm^{-1}; EIMS *m/z*: 389 (M^+), 371, 330, 298, 280, 266, 238; ^1H NMR ($CDCl_3$): δ 2.52 (2H, t, *J*=7.4 Hz), 3.01 (2H, t, *J*=7.4 Hz), 3.52 (2H, s), 3.61 (3H, s), 3.70 (3H, s), 4.55 (2H, s), 5.29 (2H, s), 7.32–7.43 (5H, m); ^{13}C NMR: 20.28, 29.41, 34.82, 51.49, 52.43, 56.10, 66.13, 114.66, 118.02 128.32, 128.42, 128.62, 130.27, 134.14, 135.93, 160.59, 173.39, 173.56; Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60%. Found: C, 61.34; H, 5.97; N, 3.65%.

3.1.9. Synthesis of pyrromethane (1c). To a solution of α-free pyrrole **2c** (48.1 mg, 0.12 mmol) and 5-mercaptobenzothiazothiazolylmethylpyrrole-2-carboxylate derivative **4c** (53.8 mg, 0.10 mmol) in dry degassed benzene (5 ml) were added CF_3SO_3Ag (38.5 mg, 0.15 mmol) and powdered Na_2HPO_4 (49.7 mg, 0.35 mmol). The mixture was stirred under nitrogen atmosphere at room temperature for 10 min. After dilution with benzene, the mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt=2.1) to give pyrromethane **1c** as a colorless crystal (75.66 mg, 98% yield); Mp 119–122°C (crystallized from MeOH–hexane); IR (KBr): 3350, 1730, 1700, 1579, 1505, 1438, 1251, 1172 cm^{-1}; FABMS *m/z* 773 (MH^+); ^1H NMR ($CDCl_3$) δ: 2.48 (2H, t, *J*=7.4 Hz), 2.59 (2H, t, *J*=6.7 Hz), 2.79 (2H, t, *J*=6.7 Hz), 3.00 (2H, t, *J*=7.4 Hz), 3.54 (3H, s), 3.59 (2H, s), 3.62 (3H, s), 3.66 (3H, s), 3.79 (3H, s), 3.87 (2H, s), 3.97 (2H, s), 4.86 (2H, s), 5.25 (2H, s), 7.29–7.35 (5H, m), 9.95 (1H, brs), 10.35 (1H, brs); ^{13}C NMR: 18.61, 20.60, 22.35, 29.42, 30.98, 34.09, 34.84, 51.49, 52.01, 52.02, 52.80, 65.83, 73.74, 95.21, 114.74, 118.05, 118.36, 120.28, 121.55, 123.65, 128.27, 128.55, 129.96, 131.76, 133.00, 136.15, 158.98, 160.62, 171.71, 173.59, 174.02, 174.55; Anal. Calcd for $C_{34}H_{37}N_2O_{12}Cl_{13}$: C, 52.90; H, 4.83; N, 3.63%. Found C, 52.69; H, 4.87; N, 3.61%. The reaction of slightly excess **4c** (1.2 equiv.) with **2c** (1 equiv.) under the similar conditions produced a symmetric pyrromethane **11** as a minor product (about 10% yield) along with major product **1c**. **11**: Mp 144–146°C (crystallized from MeOH); IR (KBr): 3320 (br), 1730, 1700, 1580, 1500, 1438, 1255, 1170 cm^{-1}; FABMS *m/z*: 731 (MH^+): ^1H NMR ($CDCl_3$) δ: 2.50 (4H, t, *J*=7.4 Hz), 3.01 (4H, t, *J*=7.4 Hz), 3.56 (4H, s), 3.59 (12H, s), 3.82 (2H, s), 5.24 (4H, s), 7.28–7.39 (10H, m); ^{13}C NMR: 20.42, 22.54, 29.35, 34.82, 51.45, 52.49, 65.75, 113.78, 118.25, 128.02, 128.38, 128.43, 129.95, 132.11, 136.23, 160.37, 173.69, 174.07; Anal. Calcd for $C_{39}H_{42}N_2O_{12}$: C, 64.09; H, 5.80; N, 3.84. Found: C, 64.13; H, 5.82; N, 3.83%.

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