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SYNTHESIS OF NEW THIOPYRYLOCYANINES INCORPORATED THIOPYRANO[2,3-*b*]INDOLE RING AS THE MAIN CONSTITUENT

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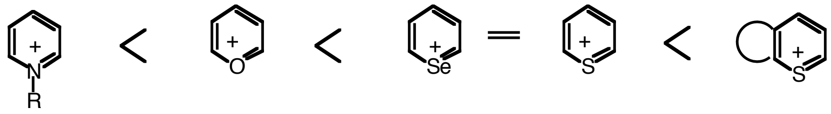
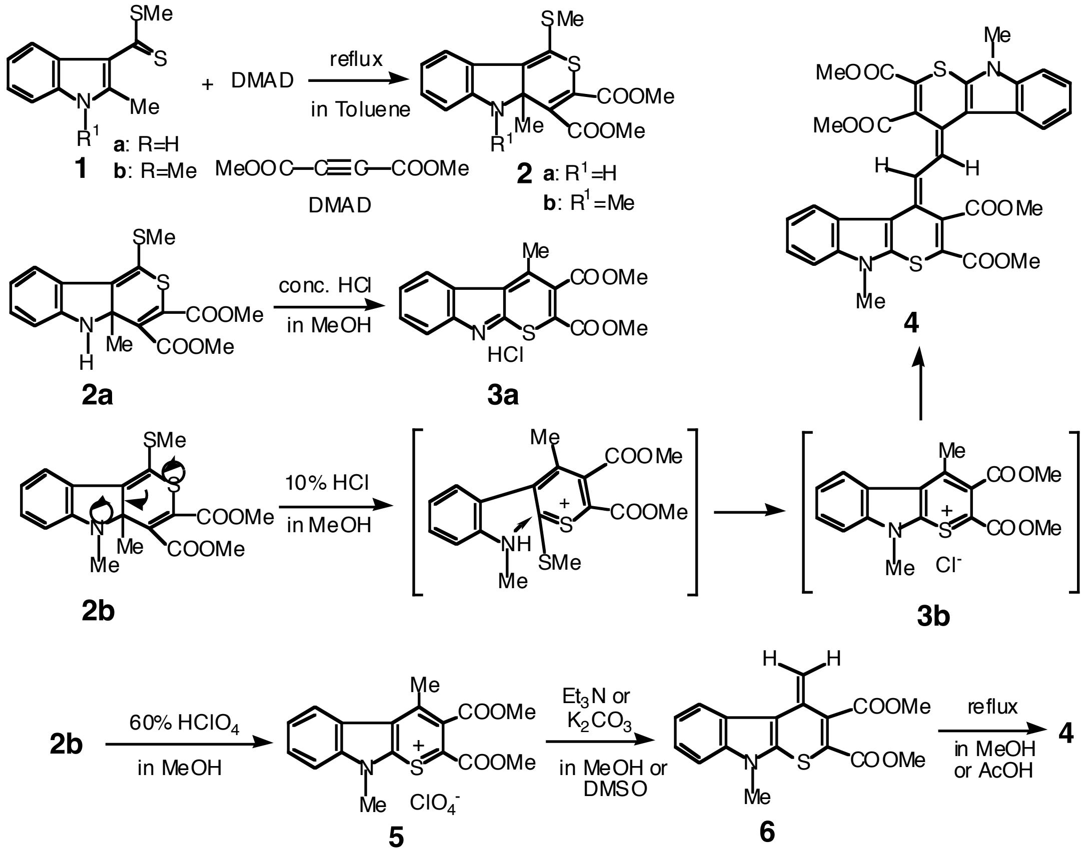
Abstract -The Diels-Alder product, dimethyl 5-methyl-4a-methyl-1-methylthiothiopyrano[4,3-*b*]indole-3,4-dicarboxylate (**2b**), which was obtained by the reaction of methyl 1,2-dimethylindole-3-dithiocarboxylate (**1b**) with DMAD (dimethyl acetylenedicarboxylate), was easily converted to a 1,5-dimethyl-2,3-bis(methoxycarbonyl)indolo[2,3-*b*]thiopyrylium perchlorate (**5**) as the key intermediate for the thiopyrylocyanine and merocyanine dyes. Compounds (**5** and **6**) were allowed to react with aromatic aldehydes and some electrophilic reagents to yield cyanine and merocyanine dyes (**8a-c**, **10-12**) in good yields.

The literature reveals that many kinds of cyanine dyes have been developed over the years, and that they have been used in various fields as photosensitizers for color photography,[1] makers for flow cytometry,[1] in the study and detection of nucleic acids,[2] and as phototherapeutic agents.[3] Asymmetric cyanine dyes consist of two different heteroaromatic fragments conjugated by a mono- or polymethine chain. By varying the length of this chain or the kind of heterocycles, the photophysical properties of these dyes can be altered. The heterocyclic ring cation that exists in the terminal of the side chain greatly influences the long wavelength absorption of the cyanine dyes. In these heterocyclic ring cations, the UV-VIS spectra of pyrylium cation show more blue shifts than those of pyridinium cation. In addition, the color of the thiopyrylium or selenopyrylium cation in the UV-VIS spectra is deeper than that of the pyrylium cation. Cyanine or merocyanine dyes, which consist of a fused thiopyrylium cation ring, will show a greater bathocromic shift in the long wavelength region in the UV-VIS spectra.

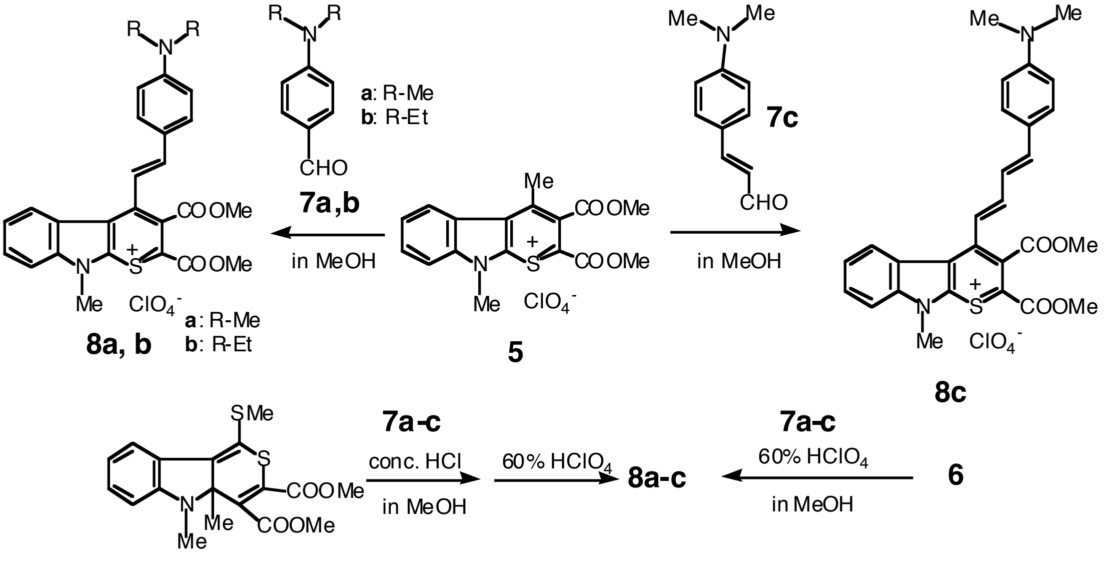


In continuation of our research program for the synthesis of polymethine dyes, we report here on the synthesis of derivatives of new thiopyrylocyanines incorporating a thiopyrano[2,3-*b*]indole ring as the main constituent.[4] The key compound in this study was a dimethyl 1-(methylene)thiopyrano[2,3-*b*]indole-2,3-dicarboxylate derivative (**6**) which was synthesized by the [4 + 2] cycloaddition reaction of methyl 2-methylindole-3-dithiocarboxylate (**1a**) with dimethyl acetylenedicarboxylate (DMAD), followed by transformation in the presence of hydrochloric acid. Previously, we reported the [4 + 2] cycloaddition reaction of methyl 2-methylindole-3-dithiocarboxylates (**1a**, **b**) with DMAD to give 4*a*-methyl-1-(methylthio)thiopyrano[4,3-*b*]indole-3,4-dicarboxylates (**2a**, **b**), wherein a thiocarbonyl group and a double bond of the 2 and 3 position exist as the diene. The treatment of **2a** with concentrated hydrochloric acid in refluxing methanol easily gave dimethyl 1-(methyl)thiopyrano[2,3-*b*]indole-2,3-dicarboxylate hydrochloride (**3a**), which could not be used for the preparation of thiopyrylocyanine. Compound (**2b**) was treated with 10% hydrochloric acid in refluxing methanol to give the dimer (**4**)^{6,7} of dimethyl 1-methylene-5-(methyl)thiopyrano[2,3-*b*]indole-2,3-dicarboxylate *via* **3b** in 66% yield. In this case, a monomer product (**6**) was not obtained. Treatment of **2b** with 60% perchloric acid afforded the expected product, 1,5-dimethyl-2,3-bis(methoxycarbonyl)indolo[2,3-*b*]thiopyrylium perchlorate (**5**)^{6,7} in 96% yield. This compound could be transformed to dimethyl 1-(methylene)thiopyrano[2,3-*b*]indole-2,3-dicarboxylate (**6**) as a free base,^{9} by treatment of **5** with a base like triethylamine in methanol or potassium carbonate in dimethyl sulfoxide in 92 or 94% yields, respectively.



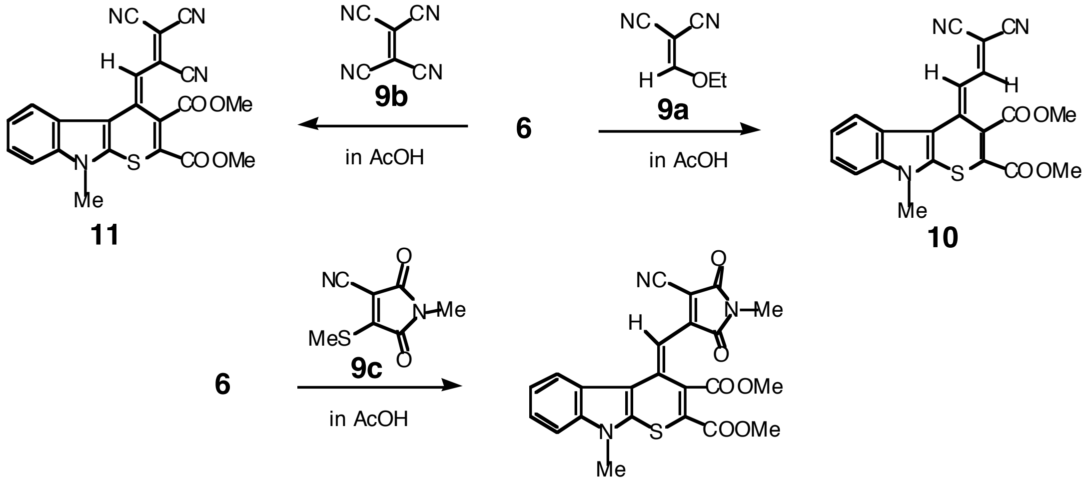
Scheme 1

This methylene compound (**6**) was smoothly converted to **4** in a good yield by refluxing in methanol or acetic acid. The reaction of **5** with 4-(*N,N*-dimethylamino)benzaldehyde (**7a**) in refluxing methanol for 2 h gave 2,3-bis(methoxycarbonyl)-1-[4-(*N,N*-dimethylamino)]styryl-5-methylindolo[2,3-*b*]thiopyrylium perchlorate (**8a**)^{10} in 78% yield. Compounds (**8b**, **c**)^{10} were also obtained in good yields by the reaction of **5** with 4-(*N,N*-diethylamino)benzaldehyde (**7b**) or 4-(*N,N*-dimethylamino)cinnamaldehyde (**7c**). These cyanines (**8a-c**) were directly prepared from **2b** in a manner similar to that described for the preparation of **8a-c** from **5**. The compounds (**8a-c**)[10] are brilliant green, showing at 710 (log ε 4.70), 704 (log ε 4.05), and 798 (log ε 4.73) nm in the UV-VIS spectra, respectively. The bathochromic shift of 94 nm at the long-wavelength band in the comparison in the UV-VIS spectra between **8a** and **8c** was observed for the addition of a double bond.



Scheme 2

Compound (**6**) should react at an exocyclic double bond with electrophilic reagents such as ethoxymethylenemalononitrile (**9a**), tetracyanoethylene (**9b**), and 4-cyano-1-methyl-3-methylthio-1*H*-pyrrole-2,5-dione (**9c**) to give the 4-substituted (methylene)thiopyrano[2,3-*b*]indole derivatives (**10-12**).



Scheme 3

The reaction of **6** with **9a** under refluxing in acetic acid gave violet leaflets (**10**)[11] in 71% yield. Compound (**6**) also smoothly reacted with **9b** under similar reaction conditions to give 4-tricyanopropenylidene (**11**)[12] as black crystals in 29% yield. The reaction of **6** with **9c** gave the corresponding merocyanine dye (**12**)[13] as black crystals in 15% yield. The maximum absorption in the long wavelength region in UV-VIS spectra of **10-12** appeared at 551 (log ε 4.33), 640 (log ε 4.45) and 645 (log ε 4.50) nm, respectively.

In conclusion, dimethyl 5-methyl-1-(methylene)thiopyrano[2,3-*b*]indole-2,3-dicarboxylate (**6**) is an important and versatile starting material as the terminal heterocyclic compound for the synthesis of new thiopyrylocyanine and merocyanine dyes.

REFERENCES AND NOTES

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6. Though the stereochemistry of the products has not been decided, the structures shown in the figure have been estimated from the NMR spectra and the result of calculation by MOPAC.
7. **4**: Dark violet leaflets, mp 312-315°C(DMF). ^{1}H-NMR (DMSO-d_6) : 3.29 (6H, s, 2xNMe), 3.81 (6H, s, 2xOMe), 3.86 (6H, s, 2xOMe), 6.30 (2H, s, C=H), 7.14 (2H, dd, J=7.4, 8.2 Hz, 7, 7’-H), 7.35 (2H, dd, J=7.4, 8.0 Hz, 8, 8’-H), 7.66 (2H, d, J=8.0 Hz, 9, 9’-H), 7.76(2H, d, J=8.2 Hz, 6, 6’-H). MS m/z: 656 (M^+).
8. **5**: Red leaflets, mp 231-234°C(MeOH). ^{1}H-NMR ($CDCl_3$+ CF_3COOD) : 3.17 (3H, s, Me), 4.13 (3H, s, NMe), 4.14 (3H, s, OMe), (3H, s, OMe), 7.77 (1H, t, J=8.2 Hz, 7-H), 7.89 (1H, d, J=8.2 Hz, 8-H), 7.96 (1H, t, J=8.2 Hz, 9-H), 8.45 (1H, d, J=8.2 Hz, 6-H).
9. **6**: Greenish yellow needles, mp 275-278°C(MeOH). ^{1}H-NMR ($CDCl_3$) : 3.74 (3H, s. NMe), 3.91 (3H, s, OMe), 3.97 (3H, s, OMe), 5.03 (1H, s, C=H), 5.76 (1H, s, C=H), 7.19-7.37 (3H, m, 6, 7, 8-H), 7.90 (1H, d, J=7.4 Hz, 9-H). MS m/z: 329 (M^+, 100),
10. **8a:** Black crystals, mp 230°C (decomp)(MeoH). Ms m/z: 462 (M^+). **8b**: balck crystals, mp 240°C (decomp), Ms m/z : 489 (M^+). **8c**: black crystals, mp 230-240°C (decomp)(MeOH), FAB MS:487 (M^++1).
11. **10:** Dark violet leaflets, mp 216-218°C(MeOH), ^{1}H-NMR ($CDCl_3$) : 3.88 (3H, s, NMe), 3.97 (3H, s, OMe), 4.04 (3H, s, OMe), 6.30 (1H, d, J=12.4 Hz, C=H), 7.22-7.44 (3H, m, 7, 8, 9-H), 7.74(1H, d, J=8.2 Hz, 6-H), 8.24 (1H, d, J=12.4 Hz, C=H).
12. **11**: Black crystals, mp 210-232°C(CH_2Cl_2), ^{1}H-NMR ($CDCl_3$) : 3.77 (3H, s, NMe), 4.03 (3H, s, OMe), 4.07 (3H, s, OMe), 6.40 (1H, s, C=H), 7.09-7.61 (4H, m, 6, 7, 8, 9-H), MS m/z: 430 (M^+).
13. **12:** Black crystals, mp 230-232°C(MeOH), ^{1}H-NMR ($CDCl_3$) : 3.14 (3H, s, NMe), 4.02 (3H, s, NMe), 4.03 (3H, s, OMe), 4.09 (3H, s, OMe), 6.64 (1H, s, C=H), 6.70 (1H, d, J=8.00 Hz, 6-H), 7.27-7.65 (3H, m, 7, 8, 9-H), MS:m/z 464 (M^+).