Pergamon

Tetrahedron Letters 39 (1998) 2365–2366

TETRAHEDRON LETTERS

2-Mercaptobenzothiazolylmethylpyrrole as a New Means for the Synthesis of Pyrromethanes under Neutral Conditions

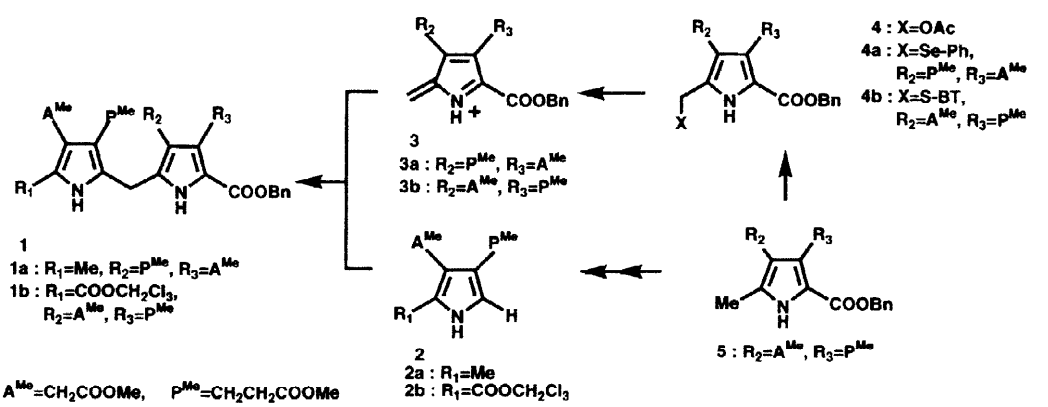
Kunisuke Okada,* Kiyoshi Saburi, Keishi Nomura and Hideo Tanino
Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468, Japan

Received 11 December 1997; accepted 19 January 1998

Abstract: The coupling reaction of 2-mercaptobenzothiazolylmethylpyrrole **4b** with α-free pyrrole **2b** in the presence of silver (I) triflate proceeds smoothly at room temperature to give pyrromethane **1b** in excellent yield. **4b** reacts rapidly with pyrromethane **1b** under similar neutral conditions to afford symmetric pyrromethane **7** in preparative yield. © 1998 Elsevier Science Ltd. All rights reserved.

Pyrromethanes **1** are usually synthesized by coupling reactions of α-acetoxymethylpyrroles **4** with α-free pyrroles **2** in the presence of protonic acids (p-TsOH, TFA, AcOH) or Lewis acid ($SnCl_4$) as catalyst.[1] The azafulvenium ion **3**, generated from **4** under these conditions, is a key intermediate in the coupling reaction with **2**. In 1991, Battersby et. al. reported phenylselenomethylpyrrole **4a** to react rapidly under mild conditions with α-free pyrrole **2a** in the presence of copper (I) triflate to form the pyrrole-CH_2-pyrrole system **1a** in preparative yields.[2] In this manner, **4a** eliminates the phenylseleno group using the copper (I) catalyst to yield the the required azafulbene intermediate **3a** as depicted in Scheme 1.

Scheme 1



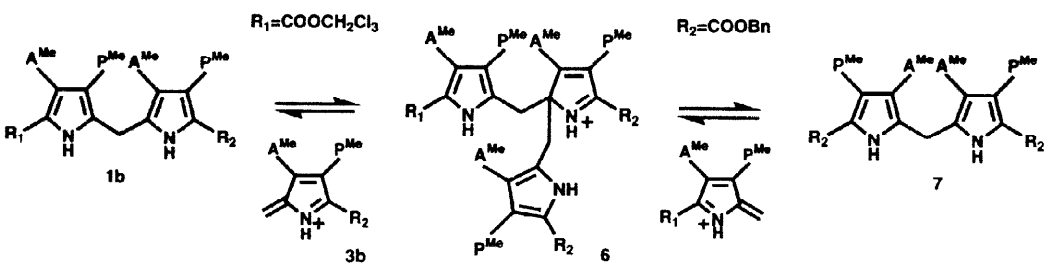
At this laboratory, attention has been directed to the chemistry of pyrromethane synthesis, particularly in regard to development of a method for the effective synthesis of bilane[3] and oligopyrroles[4] related to the interest of the biosynthetic mechanism of uroporphyrinogen III.[5] During investigation on the synthesis of pyrromethanes under mild and neutral conditions, coupling reaction between α-free pyrrole **2b** and 2-mercaptobenzothiazolylmethylpyrrole **4b** was found to proceed smoothly at room temperature using a thiophile reagent such as silver (I) triflate (AgOTf) in excellent yield.

PII: S0040-4039(98)00201-9

The required substrates **2b** and **4b** were prepared from the known benzyl 5-methylpyrrole-2-carboxylate **5**.[6] First, α-free pyrrole **2b** was prepared from **5** by the method of Battersby as follows: 1) SO_2Cl_2 then H_2O-acetone, 100 °C (73%); 2) 2,2,2-trichloroethanol-DCC-DMAP (85%); 3) H_2 / 10% Pd-C (94%); 4) I_2 / KI (86%); 5) H_2 / 10% Pd-C (97%).[7] The mercaptomethylpyrrole derivative **4b** was prepared by treatment of α-acetoxymethylpyrrole **4**[6b] derived from **5** with 2-mercaptobenzothiazole in the presence of a catalytic amount of *p*-toluenesulfonic acid in dry dichloromethane for 16 h at room temperature in 96% yield. Several preliminary experiments indicated 2-mercaptobenzothiazolylmethylpyrrole **4b** to be the most efficient substrate, compared with phenylmercaptomethyl- and *tert*-buthylmercaptomethyl-pyrrole derivatives[8] and the most efficient thiophile reagents to be AgOTf compared with AgOTFA or $Hg(OTFA)_2$. A typical procedure for coupling reaction of **2b** and **4b** is as follows. To a solution of α-free pyrrole **2b** (48.1 mg, 0.12mmol) and 2-mercaptobenzothiazolylmethylpyrrole **4b** (53.8 mg, 0.10 mmol) in dry degassed benzene (5 ml) were added AgOTf (38.5 mg, 0.15 mmol) and powdered Na_2HPO_4 (49.7 mg, 0.35 mmol). The mixture was stirred under nitrogen 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 to give pyrromethane **1b** in 98% yield calculated from **4b**.

It is of interest that the reaction of excess **4b** (1.2 equiv.) with **2b** (1 equiv.) under similar conditions gave *symmetric* pyrromethane **7** as a minor product along with **1b** at about 1:10. Pyrromethane **7** should thus be produced through intermediate **6**, generated from the cross coupling reaction of **1b** with **3b**, as shown in Scheme 2. In fact, when pyrromethane **1b** (10 mg, 13 μmol) was reacted with four equiv. **4b** (28 mg, 52 μmol) under similar conditions, **7** (7.5 mg) was isolated as the major product in addition to recovered **1b** (2.0 mg) from the equilibrated mixture. Coupling reactions of **4b** with other substrates presently being studied.

Scheme 2



References and notes

1. Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*, Academic press, 1977. 2. Hawker, C. J.; Philippides, A.; Battersby, A. R. *J. Chem. Soc. Perkin Trans. 1.* **1991**, 1833-1837. 3. Pichon, C.; Scott, A. I. *Tetrahedron Lett.* **1994**, *35*, 4497-4500. 4. Kogan, M.; Valasinas, A.; Frydman, B. *Tetrahedron Lett.* **1996**, *37*, 763-766. 5. Battersby, A. R.; Leeper, F. J. *Chem. Rev.* **1990**, *90*, 1261-1274. Scott, A. I. *Acc. Chem. Res.* **1990**, *23*, 308-317. 6. a. Valasinas, A.; Frydman, B. *J. Org. Chem.* **1976**, *41*, 2991-2994. b. Battersby, A. R.; Ihara, M.; McDonald, E.; Saunders, J.; Wells, R. J. *J. Chem. Soc. Perkin Trans 1.* **1976**, 283-291. 7. Battersby, A. R.; McDonald, E.; Hollenstein, R.; Ihara, M.; Satoh, F.; Williams, D. C. *J. Chem. Soc. Perkin Trans. 1.* **1977**, 166-178. 8. Both mercaptomethylpyrroles were prepared from **4** by the similar method to that of **4b**.