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

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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 (SnCl₄) 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-CH₂-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 bilane³ and oligopyrroles⁴ 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.

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) SO₂Cl₂ then H₂O-acetone, 100 °C (73%); 2) 2,2,2-trichloroethanol-DCC-DMAP (85%); 3) H₂ / 10% Pd-C (94%); 4) I₂ / KI (86%); 5) H₂ / 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 derivatives⁸ 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 Na₂HPO₄ (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 μ mol) was reacted with four equiv. 4b (28 mg, 52 μ mol) 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

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Both mercaptomethylpytroles were prepared from 4 by the similar method to that of 4b.