

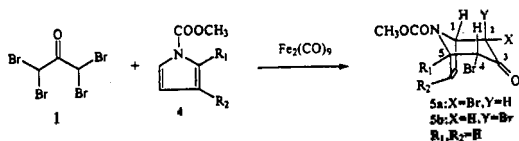
[4+3] Cycloaddition 반응에 있어서 Pyrrole 유도체에  
 포함된 작용기와 Et<sub>2</sub>Zn나 Fe<sub>2</sub>(CO)<sub>9</sub>과 같은 금속 첨가물과의 관계 연구

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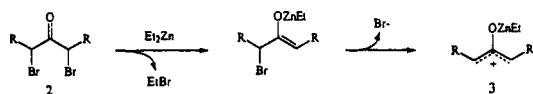
Relationship Study between Functional Groups on Pyrrole Derivatives  
 and Additive Metals such as Et<sub>2</sub>Zn and Fe<sub>2</sub>(CO)<sub>9</sub>  
 in [4+3] Cycloaddition Reactions

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Tropane alkaloids have received a great deal of attention because of their remarkable pharmaceutical significances.<sup>1</sup> Therefore, a variety of synthetic approaches to the manufacture of tropane alkaloids have been investigated.<sup>2</sup> Among these, the most widely accepted strategy is [4+3] cycloaddition between pyrrole derivatives and oxyallyls, called Noyori cycloaddition<sup>3</sup> (Scheme 1). The required oxyallyls are prepared from  $\alpha,\alpha,\alpha'$ -tetrabromoacetone (1)<sup>4</sup> by treatment with nonacarbonyldiiron (Fe<sub>2</sub>(CO)<sub>9</sub>). However, this method has three disadvantages. First, our study revealed that this method does not allow the production of an acceptable yield of functionalized tropane alkaloid.



Scheme 1.



Scheme 2.

This result will be discussed in the later part of this paper. Second, tetrabromoacetone (1), a highly lachrymatory reagent, needs to be used in large amounts. Third, the key reagent, Fe<sub>2</sub>(CO)<sub>9</sub>, is not only expensive but also toxic.

Recently, a new methodology for the preparation of oxyallyls was reported by John Mann's group<sup>5</sup> utilizing  $\alpha,\alpha'$ -dibromo ketones (2) to produce oxyallyl carbocation (3) via the mechanism shown in Scheme 2. Although this strategy provided nonfunctionalized tropane in relatively good yield (52%), it never worked for the synthesis of functionalized tropane derivatives. Since most of the naturally occurring tropane alkaloids have functionalized substituents, it is very important to study a relationship between functionalized pyrroles and the yields of [4+3] cycloaddition reactions which can eventually produce functionalized tropane alkaloids. Furthermore, introduction of functionalities is absolutely necessary for the synthesis of highly complicated tropane based molecules.

RESULTS AND DISCUSSION

In this paper we report the results of [4+3] cycloaddition between tetrabromoacetone (1) and functionalized pyrrole derivatives (4). Each reac-

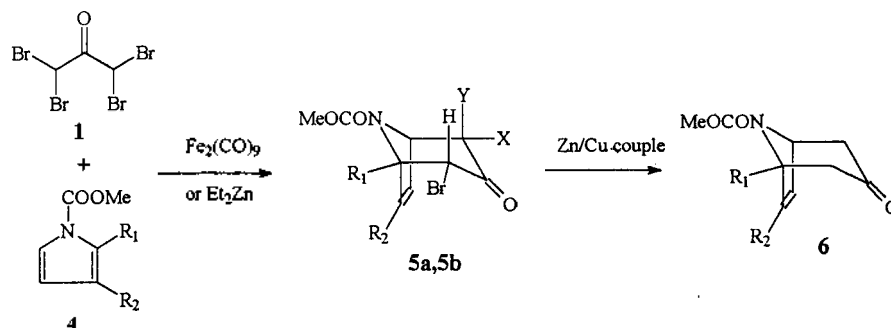


Table 1.

Entry	$\text{R}_1$	$\text{R}_2$	Yield of compound 6 (%)	
			$\text{Fe}_2(\text{CO})_9$	$\text{Et}_2\text{Zn}$
1	H	H	48	52
2	$-(\text{CH}_2)_2\text{OTBS}^{\text{c}}$	H	11	58
3	$-(\text{CH}_2)_2\text{O}_2\text{CCH}_2\text{COMe}$	H	decomposed	65
4	$-(\text{CH}_2)_2\text{OCO}_2\text{Et}$	H	decomposed	62
5	$-n\text{-Bu}^{\text{d}}$	H	15	74
6	H	$-(\text{CH}_2)_2\text{OTBS}^{\text{c}}$	7	63
7	H	$-(\text{CH}_2)_2\text{O}_2\text{CCH}_2\text{COMe}$	decomposed	61
8	H	$-(\text{CH}_2)_2\text{OCO}_2\text{Et}$	decomposed	53
9	H	$-n\text{-Bu}^{\text{d}}$	13	69

tion was run under  $\text{Fe}_2(\text{CO})_9$  or  $\text{Et}_2\text{Zn}$  mediated conditions and the resulting yields were recorded after debromination of dibromotropane (5a, 5b) under a Zn/Cu couple.<sup>6</sup>

The [4+3] cycloaddition reaction of tetrabromoacetone (1) and N-carbomethoxy pyrrole in benzene gave a 2 : 1 mixture of the desired cycloadduct 5a and 5b. Both diastereomers were quite stable during usual workup and silica gel chromatography. The stereochemistry of these isomers was verified on the basis of the NMR signals produced by the CHBr protons. The *cis* isomer 5a showed a two-proton doublet ( $J=4.0$  Hz) at  $\delta$  4.80, indicating the presence of two equivalent methine protons at C2 and C4, whereas the *trans* isomer 5b exhibited two one-proton doublets at  $\delta$  4.27 ( $J=2.0$  Hz) and  $\delta$  5.11 ( $J=3.5$  Hz) arising from the two nonequivalent methine protons. All of the debrominated products except nonfunctionalized cycloadduct (entry 1 at Table 1) were identified by mass spectroscopy and the characteristic C1 proton NMR peaks which appeared around  $\delta$  4.8,

because most of the proton signals overlapped within a range of  $\delta$  0.7~3.5 as a multiplet. The C5 side chain ( $\text{R}_1$ ) especially makes the molecule very rigid which results in extremely complicated proton NMR signals. For this reason, identification of each proton based on NMR signal was impossible.

As shown on Table 1, [4+3] cycloaddition between oxyallyls and nonfunctionalized pyrrole produced a high yield of tropane derivatives regardless of use of  $\text{Fe}_2(\text{CO})_9$  or  $\text{Et}_2\text{Zn}$  (entry 1). When oxyallyl was reacted with functionalized pyrrole derivatives, the results are far different however, according to the use of  $\text{Fe}_2(\text{CO})_9$  or  $\text{Et}_2\text{Zn}$  (entry 2-9). While  $\text{Fe}_2(\text{CO})_9$  mediated reactions afforded only a miserable yield of desired tropane products with a decomposed base spot on TLC, the  $\text{Et}_2\text{Zn}$  mediated reaction provided good isolated yields. This means that many functional groups can initiate the decomposition of either pyrrole derivatives or cycloadducted products.

## EXPERIMENTAL

All spectra were performed at the University of Rochester in U.S.A. IR spectra were recorded with a Perkin-Elmer 881 double beam grating spectrophotometer. NMR were recorded with a Bruker WH 300 spectrometer (300 MHz) in  $\text{CDCl}_3$ .  $J$  values are given in Hz. Mass spectra were obtained on an A.E.I. Ms12 spectrometer. E. Merck GF 254 silica gel plate (0.25 mm) was used for TLC. Column chromatography was performed with the aid of a kieselgel 60 (70~230 mesh). Solvents were purified according to Perrin.<sup>9</sup> Tetrabromoacetones, *N*-carbomethoxypyrrole and Zn/Cu couple were prepared by the known procedure.  $\text{Fe}_2(\text{CO})_9$  and  $\text{Et}_2\text{Zn}$  were purchased from Aldrich Chemical Co. and used directly under an argon atmosphere.

**Reaction of *N*-carbomethoxypyrrole and tetrabromoacetone with  $\text{Fe}_2(\text{CO})_9$ .** Into  $\text{Fe}_2(\text{CO})_9$  (1.09 g, 3.00 mmol) was poured a solution of tetrabromoacetone (1, 1.13 g, 3.00 mmol) in benzene (7.5 mL). The mixture was heated at 50 °C with continuous stirring for 5 min. To the resulting mixture was added *N*-carbomethoxypyrrole (125 mg, 1.00 mmol) and then the mixture was allowed to stand at the same temperature with constant stirring for 72 h. The dark brown reaction mixture was diluted with ethyl acetate (15 mL) and the remaining insoluble materials were removed by filtration through a Celite 545 pad. The filtrate was concentrated under reduced pressure leaving a black, tarry residue. Preparative TLC of the tar with 1 : 3 ethyl acetate-hexane afforded a mixture of **5a** and **5b** in 52% yield (145 mg).

**Reaction of *N*-carbomethoxypyrrole and tetrabromoacetone with  $\text{Et}_2\text{Zn}$ .** A solution of tetrabromoacetone (1, 11.22 g, 30 mmol) and *N*-carbomethoxypyrrole (3.75 g, 30 mmol) in dry benzene (600 mL) was cooled to 0 °C, and to this was added a diethylzinc (1 M in hexane, 30 mL, 30 mmol) over a period of 1 h. The resultant mixture was stirred for a further 3 h at 0 °C then at room temperature for 19 h. The reaction was quenched by addition of ethyl acetate (200 mL) and a saturated solution of  $\text{Na}_2\text{EDTA}$  (150 mL). The two layers

were separated and the organic phase was washed with saturated  $\text{Na}_2\text{EDTA}$  (50 mL) and brine (50 mL) and then dried ( $\text{MgSO}_4$ ). After concentration under reduced pressure the crude cycloadduct was purified by gradient column chromatography with elution of diethyl ether and hexane. Crude products consisting of substituted dibromotropene derivatives are directly used for debromination reactions without any further purification.

compound **5a** (entry 1). IR: 1748, 1710  $\text{cm}^{-1}$ . NMR:  $\delta$  3.82 (s, 3H), 4.80 (d,  $J=4.0$ , 1H), 5.11 (dd,  $J=1.0$ , 4.0, 1H), 5.0-5.3 (dd,  $J=1.0$ , 4.0, 1H), 6.53 (t-like,  $J=1.0$ , 1H). Mass,  $m/e$ : 341.

compound **5b** (entry 1). IR: 1740, 1710  $\text{cm}^{-1}$ . NMR:  $\delta$  3.82 (s, 3H), 4.27 (d,  $J=2.0$ , 1H), 5.11 (d,  $J=3.5$ , 1H), 5.0-5.3 (m, 1H), 6.36 and 6.61 (dd,  $J=2.0$ , 6.0, 1H each). Mass,  $m/e$ : 341.

**Debromination reaction with Zn/Cu couple.** The crude dibromotropenes (**5a**, **5b**) obtained from  $\text{Et}_2\text{Zn}$  reaction was dissolved in a saturated methanolic solution of  $\text{NH}_4\text{Cl}$  (120 mL) and freshly prepared Zn/Cu couple (18 mg) was added portionwise. The mixture was stirred at room temperature for 2.5 h, then the solid was removed by filtration through a Celite pad. The filtrate was concentrated under reduced pressure to remove some of the methanol, and subsequently diluted with dichloromethane (200 mL) and washed with  $\text{Na}_2\text{EDTA}$  solution ( $2 \times 50$  mL). The combined aqueous phase was extracted with dichloromethane ( $3 \times 50$  mL). The organic extract was then dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to leave the crude cycloadduct as a brown oil. This oil was purified by flash chromatography on silica gel using ethyl acetate-light petroleum (2 : 3) to afford the required cycloadduct **6** (entry 1) in 58.5% yield (3.17 g, 17.5 mmol).

IR: 3005, 1710  $\text{cm}^{-1}$ . NMR:  $\delta$  2.40 (dd,  $J=16.5$ , 1.5, 2H), 2.80 (dd,  $J=16.5$ , 4.5, 2H), 3.84 (s, 3H), 4.90 (br d,  $J=4.5$ , 1H), 6.27 (t-like,  $J=1.0$ , 1H). Mass,  $m/e$ : 182.

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