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# Trimethoprim 중간체인 Diethyl 3, 4, 5-Trimethoxybenzylmalonate 의 새로운 합성

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# A New Route to Diethyl 3, 4, 5-Trimethoxybenzylmalonate, a Trimethoprim Intermediate

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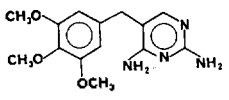
**요 약.** 3, 4, 5-Trimethoxybenzoyl chloride와 diethyl malonate를 축합시킨후, 염소화반응 및 가수소화 분해 반응을 거쳐 diethyl 3, 4, 5-trimethoxybenzylmalonate를 70%의 수득율로 합성하였다.

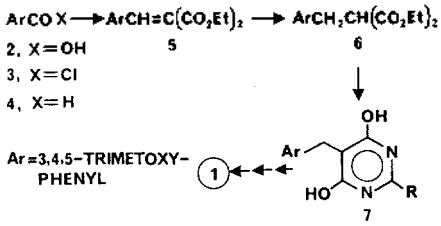
**ABSTRACT.** Direct condensation of 3, 4, 5-trimethoxybenzoyl chloride with diethyl malonate followed by chlorination and hydrogenolysis afforded diethyl 3, 4, 5-trimethoxybenzylmalonate in 70 % overall yield.

## INTRODUCTION

The significant antibacterial activities of trimethoprim (**1**)[1], 5-(3, 4, 5-trimethoxyphenylmethyl)-2, 4-pyrimidinediamine, and its analogues[2] have provided continueous impetus to develop new synthetic methods. Of numerous syntheses developed so far, the simplest one involves the reaction of 3, 4, 5-trimethoxybenzaldehyde (TMBA) (**4**)[3] with $\beta$-substituted propionitrile followed by guanidine[1c,4], although coupling of phenolic Mannich base with pyrimidine derivatives has recently been introduced[5].



Another route to trimethoprim also started from TMBA (**4**), which was condensed with more active methylene compounds such as diethyl malonate[6], malononitrile[7] or ethyl cyanoacetate[8]. One noteworthy example is the reaction of diethyl malonate with TMBA as illustrated in *Scheme* **1**[6]. Hydrogenation of the condensation product **5** afforded a key intermediate, diethyl 3, 4, 5-trimethoxybenzylmalonate (**6**), which was treated with guanidine or urea to produce the hydroxypyrimidine derivatives **7** (R=$NH_2$ or OH). Chlorination of the compounds **7** with phosphoryl chloride and subsequent transformation of the resulting compounds to 2, 4-diamino-6-chloropyrimidine derivative followed by hydrogenolysis of the 6-chloro group furnished trimethoprim (**1**) in excellent yield[6~8].




*Scheme* 1.

In these as well as in most other syntheses of trimethoprim, the starting point was TMBA (**4**), which was prepared in variable yield from 3, 4, 5-trimethoxybenzoic acid (**2**) by chlorination[9] and reduction[3]. In place of such a difficultly available TMBA, we have taken advantage of readily accessible 3, 4, 5-trimethoxybenzoyl chloride (**3**) as a starting material and developed a new and efficient synthetic method for a trimethoprim intermediate, diethyl 3, 4, 5-trimethoxybenzylmalonate (**6**).

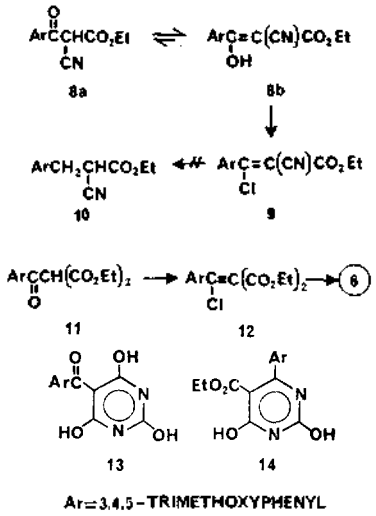
## RESULTS AND DISCUSSION

Base-assisted condensation of the acid chloride **3** with ethyl cyanoacetate or diethyl malonate furnished the condensation products **8** and **11** in excellent yield. Nmr and ir spectra of these compounds clearly indicated that the cyano derivative **8** exists mainly in enol form **8b** rather than keto form **8a**, whereas the malonate **11** does exist in keto form.

Chlorination of the cyano derivative **8b** with phorphorus pentachloride in dimethylformamide[10] readily afforded the chloro compound **9** within an hour, but hydrogenolysis of this compound **9** with hydrogen over Pd-C produced many products, probably due to the progressive reduction of the cyano group, thus the pure cyano derivative **10** could not be isolated.

Condensation reaction of the malonate **11** with urea proceeded smoothly, but the undesired arylpyrimidine derivative **14** was obtained in excellent yield instead of the trimethoprim derivative **13**, the keto group of which could be transformed into various functional groups (see *Scheme 2*).

Chlorination of the malonate **11** with phosphorus pentachloride in dimethylformamide[10] proceeded smoothly, even if higher reaction temperature and longer reaction period were required, compared to the chlorination of the




*Scheme 2.*

cyano derivative **8**. The chlorinated product **12** was then reduced by $H_2$/Pd-C to diethyl 3, 4, 5-trimethoxybenzylmalonate (**6**), which can be efficiently transformed in three known steps[6~8] into the biologically active trimethoprim (**1**).

## EXPERIMENTAL

Melting points were determined on a Mettler FP-5 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were obtained on a Varian EM-360 (60 MHz) spectrometer and chemical shifts are reported in parts per million downfield from internal standard of tetramethylsilane. Infrared spectra were recorded on a Beckmann Acculab-4 spectrophotometer. All the chemicals used were of reagent grade and purified prior to use if necessary.

**3, 4, 5-Trimethoxybenzoyl chloride** (**3**) was prepared in 88% yield from 3, 4, 5-trimethoxybenzoic acid (**2**) and thionyl chloride by the literature procedure[9], mp 79~80°C (lit.[9] 79~81°C). $^1$H-NMR ($CDCl_3$): $\delta$ 7.10 (s, 2H, phenyl), 3.90 (s, 9H, three $OCH_3$). IR (KBr): 1760cm$^{-1}$ (acid chloride).

**Ethyl 2-cyano-3-(3, 4, 5-trimethoxybenzo-**

**yl)propionate (8)**. To a solution of ethyl cyanoacetate (1.13g, 10 mmole) in benzene (40 m*l*) was added sodium metal (0.23g, 10mmole) and the mixture was refluxed until sodium reacted completely. To the cooled solution was added a benzene solution (20m*l*) of the acid chloride **3** (2.31g, 10mmole) and the mixture was stirred at room temperature for 2 hr. The suspension was extracted with ice-water (50 m*l*) and the aqueous solution was washed with diethyl ether. After the aqueous solution was acidified with 6N hydrochloric acid, the sticky residue was extracted with benzene. Evaporation of benzene after drying over anhydrous sodium sulfate left a solid which was washed with methanol, mp 125°C, yield: 2.3g (75%). $^1$H-NMR ($CDCl_3$): $\delta$ 14.3 (s, 1H, enolic OH, $D_2O$ exchangeable), 7.35 (s, 2H, phenyl), 4.38 (q, J=7.0 Hz, 2H, $CH_2$), 3.88 (s, 9H, three $OCH_3$), 1.45 (t, J=7.0 Hz, 3H, $CH_3$). IR (KBr): 3600~3200 (broad, hydroxyl), 2210 (nitrile), 1650cm$^{-1}$ (ester).

**Ethyl 2-cyano-3-chloro-3-(3,4,5-trimethoxyphenyl)propenoate (9)**. To a suspension of the above compound **8** (3.07g, 10mmole) in dry dimethylformamide (10m*l*) was added phosphorus pentachloride (2.3g, 11 mmole) and the mixture was stirred at 60°C for 1 hr. Ice-water (100m*l*) and diethyl ether (200m*l*) were added and the organic layer was washed with 10% aqueous sodium bicarbonate and water. Drying and evaporation of the ether solution gave a yellow solid which was recrystallized from methanol, mp 124~125°C, yield: 2.47g (76%). $^1$H-NMR ($CDCl_3$): $\delta$ 7.03 (s, 2H, phenyl), 4.35 (q, J=7.0Hz, 2H, $CH_2$), 3.90 (s, 9H, three $OCH_3$): 1.42(t, J=7.0 Hz, 3H, $CH_3$). IR (KBr): 2210 (nitrile), 1730cm$^{-1}$ (ester).

**Diethyl 3,4,5-trimethoxybenzoylmalonate (11)** was prepared from the acid chloride **3** and diethyl malonate by following exactly the same procedure for the preparation of the cyano derivatve **8**, mp 81~82°C, yield: 84%. $^1$H-NMR ($CDCl_3$): $\delta$ 7.20 (s, 2H, phenyl), 5.25 (s, 1H, CH), 4.32 (q, J=7.0Hz, 4H, two $CH_2$), 3.90 (s, 9H, three $OCH_3$), 1.31 (t, J=7.0 Hz, 6H, two $CH_3$). IR (KBr): 1735, 1730 (ester), 1700cm$^{-1}$ (ketone).

**5-Carbethoxy-2,4-dihydroxy-6-(3,4,5-trimethoxyphenyl)pyrimidine (14)**. An ethanol solution (70m*l*) of diethyl 3,4,5-trimethoxybenzoylmalonate (**11**) (7.08g, 20 mmole), sodium ethoxide (20 mmole) and urea (1.20g, 20 mmole) was refluxed for 5 hr and cooled to room temperature. After addition of ice-water (200m*l*), the aqueous solution was acidified with 6N hydrochloric acid to pH 6 and evaporated in vacuo. The residue was dissolved in benzene (100m*l*), washed several times with water, dried and evaporated to colorless solid, mp 57~58°C, yield: 5.95g(85%). $^1$H-NMR ($CDCl_3$): $\delta$ 7.30 (s, 2H, phenyl), 4.35 (q, J=7.0 Hz, 2H, $CH_2$), 3.91 (s, 9H, three $OCH_3$), 1.34 (t, J=7.0 Hz, 3H, $CH_3$). IR (KBr): 3600~3300 (broad, hydroxyl), 1720cm$^{-1}$ (ester).

**Ethyl 2-carbethoxy-3-chloro-3-(3,4,5-trimethoxyphenyl)propenoate (12)**. A solution of 3,4,5-trimethoxybenzoylmalonate (**11**) (3.54 g, 10 mmole) and phosphorus pentachloride (2.5 g) in dry dimethylformamide (20m*l*) was refluxed for 1 hr, cooled to room temperature and diluted with diethyl ether (150m*l*). The solution was washed several times with ice-water and 5% aqueous sodium bicarbonate, dried and evaporated to afford 3.10g (83% yield) of oily product which was chromatographically pure. $^1$H-NMR ($CDCl_3$): $\delta$ 6.75 (s, 2H, phenyl), 4.25 (q, J=7.0 Hz, 4H, two $CH_2$), 3.86 (s, 9H, three $OCH_3$), 1.35 (t, J=7.0 Hz, 6H, two $CH_3$). IR ($CHCl_3$): 1725cm$^{-1}$ (ester).

**Diethyl 3, 4, 5-trimethoxybenzylmalonate**

(6). The above chloro compound **12** (1.87g, 5 mmole) was dissolved in ethanol (30m*l*) and 10% palladium on charcoal (3.0g) was added. The mixture was hydrogenolyzed at the hydrogen pressure of 50 psi at room temperature for 4 hr and the solid material was removed by filtration. Evaporation of solvent left a solid which was recrystallized from methanol, mp 78~79°C (lit.[6] 78~78.5°C), yield: 1.61g (95%). $^1$H-NMR ($CDCl_3$): $\delta$ 6.55(s, 2H, phenyl), 4.12 (q, J=7.0Hz, 4H, two $CH_2$), 3.90 (s, 9H, three $OCH_3$), 3.45 (t, J=7.5 Hz, 1H, CH), 3.02 (d, J=7.5 Hz, 2H, benzylic $CH_2$), 1.20 (t, J=7.0 Hz, 6H, two $CH_3$). IR (KBr): 1730cm$^{-1}$ (ester).

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