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Studies on New Additions to 5-Methoxy-2 (5H)-Furanone: 1, 4-Addition of Grignard Reagents, and 1,3-Dipolar Cycloaddition of Silyl Nitronates

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Abstract: 1,4-Addition reaction of Grignard's reagent to 5-methoxy-2(5H)-furanone **1** was accomplished, which provided a new possible route for synthesizing β-alkyl-γ-alkyloxy-γ-butyrolactone. A novel concise method of preparing fused heterocyclic compounds was offered by 1,3-dipolar cycloaddition reaction of silyl nitronates to **1**.

Keywords: Michael addition, Grignard reagent, 1,3-dipolar cycloaddition, silyl nitronates.

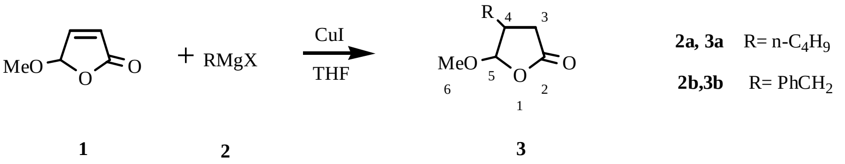
Recently, much effort has been made in the development of generally applicable organic synthesis of 5-alkyloxy-2(5H)-furanones due to their essential structure entities in the synthesis of some biologically active natural products and their application as useful intermediates in organic synthesis[1]. Their reactions such as Michael addition, Diels-Alder reaction and photocatalyzed conjugate addition have been studied extensively[2-4].

However, Michael addition reaction of Grignard reagents to 5-methoxy-2(5H)-furanone **1** and 1,3-dipolar cycloaddition reaction of silyl nitronates to **1** has not been reported yet. To continue our study on this respect, we synthesized two β-alkyl- γ-methoxy-γ-butyrolactones (**3a** and **3b**) by Michael addition reaction of Grignard reagents **2 (Scheme 1)**, and three fused heterocyclic compounds **5** by 1,3-dipolar cycloaddition reaction of silyl nitronates **4** to **1 (Scheme 2)**.

1,4-Addition of Grignard reagents 2 to 5-methoxy-2(5H)-furanone 1(Scheme 1)

For the Michael additional reaction of Grignard reagents to α,β-unsaturated esters, rigorous reaction conditions such as lower reaction temperature[5] and copper (I) salt as a catalyst[6] were often needed. Furthermore side reactions were always accompanied. 5-methoxy-2(5H)-furanone **1**, with multi-functional groups, is more difficult to achieve clean Michael addition reactions. We have found a convenient way to perform this reaction.

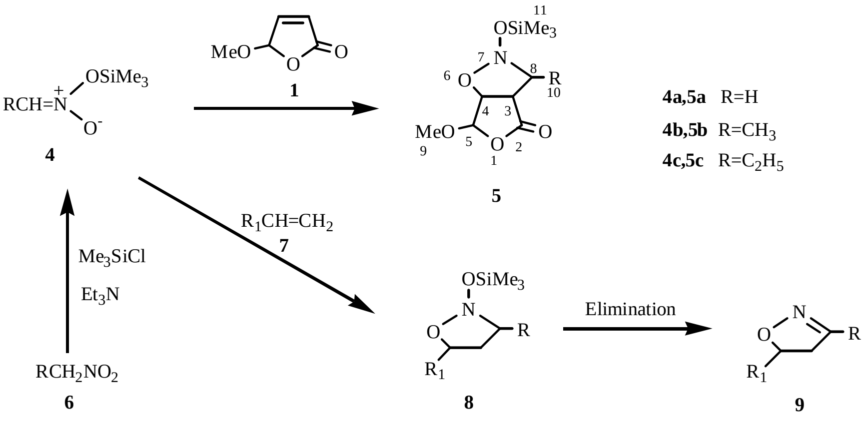
Scheme 1



The synthesis of **3a**: To a flame dried flask under nitrogen were added absolute anhydrous THF (30mL). At－78℃, the newly-prepared Grignard reagents **2a** (produced by 35mmol n-butyl bromide)and then the solution of **1**(5mmol) in THF (2~3mL)was injected in successively. After stirring for 6 hr, the mixture was worked up with saturated NH_4Cl solution, then extracted with ethyl ether. After removal of the solvents *in vacuo*, the crude product was purified by column chromatography to give a colorless liquid product **3a** in 35% yield[7].

It is noticeable that, the ring opening reaction occurred when CuI was used as a catalyst alone. In order to improve the selectivity of the 1,4-addition reaction, DMAP was used together with CuI as catalysts. LiCl was added to increase the solubility of CuI in THF. In the solution, two metal compounds existed as a complex CuX_3Li_2[8]. By this way, the yield of 1,4-addition of Grignard reagents to **1** could be increased by 10%.

Scheme 2



1,3-dipolar cycloaddition of 5-methoxy-2(5H)-furanone 1 with silyl nitronates 4 (Scheme 2)

Due to Huisgen's important contribution to the 1,3-dipolar cycloaddition reactions in the 1960s, 1,3-dipoles have been widely used in organic synthesis[9]. In the last two decades, a new kind of dipoles - silyl nitronates **4** and their cyclized adducts (eg. isoxazolindines **8** and isoxazolines **9**) were studied extensively[10].

In present paper, we describe a new aspect in this field by synthesizing another isoxazolindines— fused heterocyclic compounds **5**[11], which can be used to synthesis many other important intermediates. More importantly, if the racemic **1** is replaced by chiral synthons such as 5-(*l*)-menthyloxy-2(5H)-furanone in the 1,3-dipolar cycloaddition reaction with silyl nitronates **4**, optically active fused heterocyclic compounds could be achieved easily, which might be useful in the synthesis of some biologically active compounds. Further studies are in progress.

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References and Notes

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7. IR (liquid film): ν = 2958, 2932, 2859, 1786, 1194, 1158, 1116, 942 cm^{-1}; ^{1}HNMR (200MHz, $CDCl_3$ δ ppm): 0.9~1.6 (9H, m, n-butyl's H), 2.2 (2H, m, H-3), 2.8 (1H, dd, J = 13.6, 8.2 Hz, H-4), 3.5 (3H, s, H-6), 5.1 (1H, s, H-5); ^{13}C NMR (50MHz, $CDCl_3$ δ ppm): 13.6, 22.2, 28.8, 31.5, 33.3, 41.1, 56.6, 109.5, 175.6; MS (*m/z*): 173 (M+1, 10), 171 (M-1, 15), 141 ($C_8H_{13}O_2^+$, 15), 84 ($C_4H_4O_2^+$, 51), 71 ($C_3H_3O_2^+$, 100), 56 ($C_4H_8^+$, 43), 41 ($C_3H_5^+$, 46); Anal. Calcd. for $C_9H_{16}O_3$: C 62.76, H 9.36; Found: C 63.02, H 9.45.
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11. Synthesis of **5b**: Under nitrogen, **1** (10 mmol) was dissolved in anhydrous benzene, then trimethylchlorosilane (11mmol), triethylamine (11 mmol), and nitroalkanes **6b** (11 mmol)

were added. The reaction mixture was stirred at room temperature for 2 hr. After removing triethylamine hydrochloride salt by filteration and benzene was removed *in vacuo*, the crude product was purified by column chromatography to give a colorless crystal **5b** in 42% yield. m.p.78~79℃. IR (KBr): ν = 2980, 2940, 1785, 1132, 950, 852 cm^{-1}; ^{1}HNMR (300MHz, $CDCl_3$ δ ppm): 0.18 (9H, s, H-11), 1.4 (3H, d, J = 6.3Hz, H-10), 3.3~3.6 (5H, m, H-3、H-8、H-9), 4.9 (1H, d, J = 7.2Hz, H-4), 5.3 (1H, s, H-5); ^{13}C NMR (75MHz, $CDCl_3$ δ ppm): -0.003, 15.1, 52.7, 57.6, 73.2, 86.1, 106.6, 176.1; MS (*m/z*): 261 (M^+, 20), 116 ($C_5H_8O_3^+$, 45), 733 ($C_3H_9Si^+$, 100), 83 ($C_4H_3O_2^+$, 15), 55 ($C_3H_3O^+$, 43); Anal. Calcd. for $C_{10}H_{19}NO_5Si$: C 45.96, H 7.33, N 5.36; Found: C 45.65, H7.31, N 5.07.

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