REACTION OF 2,4,6-TRIMETHYLPYRYLIUM SALT WITH ORGANOCOPPER REAGENTS: SELECTIVE SYNTHESIS OF 4H-PYRANS

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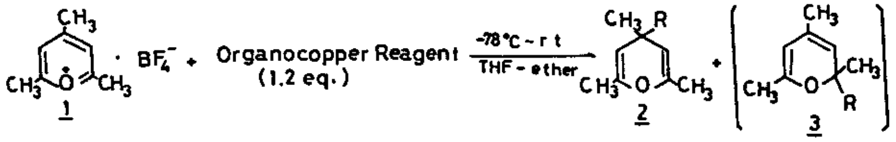
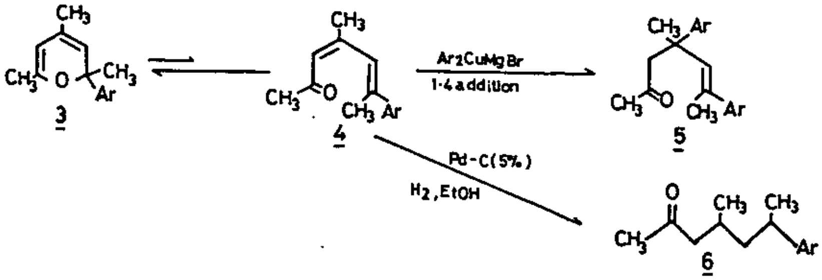
Abstract- Various cuprates (R_2CuLi or $R_2CuMgBr$) reacted with 2,4,6-trimethylpyrylium tetrafluoroborate (1) at 4-position to give 4H-pyrans with good regioselectivity (4H-:2H- $\geq$ 7:3) in high total yield (75-90 %). One-pot transformation of 4H-pyrans into cyclohexenones is also described.

It is well known that pyrylium salts react readily with nucleophiles at C-2, C-4 and/or C-6 positions to form the corresponding adducts. The reactivity of pyrylium salts varies considerably according to the substituents at the position of 2, 4, and 6, and also to the reactivity of nucleophiles.[1] For example, it has been reported that Grignard reagents[2] and organolithiums[3] react with 2,4,6-trimethylpyrylium perchlorate to afford mainly the corresponding 2H-pyrans accompanied by 4H-pyrans. Hence, it has been difficult to obtain 4H-pyrans from the corresponding pyrylium salt with high selectivity. On the other hand, we have recently developed facile and useful methods for regioselective introduction of functional groups to pyridinium salts by the use of soft nucleophiles, i.e., silyl enol ethers[4], cuprates[5] and $RCu\cdot BF_3$.[6] Thus we tried to extend our method to the regioselective synthesis of 4H-pyrans via pyrylium salts. Here we report the reaction of $R_2CuMgBr$ and R_2CuLi with 2,4,6-trimethylpyrylium tetrafluoroborate (1) (eq. 1). In a typical experiment, a suspension of 1 (6.0 mmol) in THF (30 ml) was added to a THF solution of cuprate (7.2 mmol, 35 ml) at -78 °C under nitrogen atmosphere with stirring and the reaction mixture was warmed to room temperature and then poured onto ice-water. The mixture was filtered through celite and the celite was washed with ether (200 ml). The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$, and evaporated to give the crude product. Flash column chromatography of the residue on silica gel (hexane as eluent) gave the corresponding 4H-pyran (2),[7] but 2H-pyran (3) could not be isolated probably due to decomposition during the purification.[8] In order to determine the ratio of 4H-pyran/ 2H-pyran, we carried out hydrogenation of the crude product with 5% Pd-C as a catalyst (entry 1 and 3; eq. 2). A mixture of the crude product and 5% Pd-C was stirred under hydrogen atmosphere until a theoretical amount of hydrogen had been absorbed. The catalyst was filtered and the solvent was removed to give the crude hydrogenated product. A saturated ketone (6a)[9] was obtained in 17% yield by preparative TLC (SiO_2, hexane: AcOEt= 17:3) together with 4H-pyran (2a: 73%) when $(p\text{-Tolyl})_2CuLi$ was used. Hence, we determined the product ratio on the basis of the yield of 2 and 6 (entry 1 and 3). When an alkylcopper reagent was used, a complex mixture containing 2 and 6 was obtained after the hydrogenation. The ratio of 2 and 3 could be determined from the ^{1}H-nmr spectrum of the crude product before the hydrogenation, i.e., a singlet at δ 4.52 was assigned to the vinyl proton of 2 and multiplets at δ 4.65-4.82 were assigned to that of 3 (entry 6-9).[2] On the other hand, in the case of $Ar_2CuMgBr$, we found that selective 1,4-addition reaction of excess

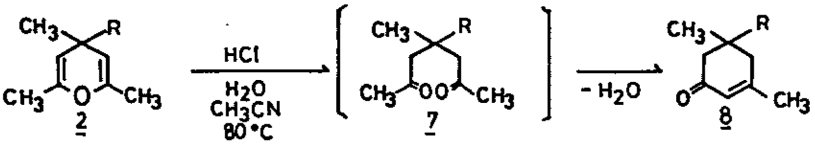


(1)

2,3: a) R= p-Tolyl, b) R= p-Anisyl, c) R= p-ClC_6H_4, d) R= n-Octyl, e) R= Phenethyl



(2)



(3)

cuprate to cis-diene (4), which existed in equilibrium with 2H-pyran (3) (eq. 2),[10] took place to give γ,δ-unsaturated ketone (5)[11] which was isolated by flash chromatography on silica gel (hexane: AcOEt= 9:1, as eluent). Thus, we calculated the product ratio on the basis of the yields of 2 and 5. The representative results are collected in the Table 1. Especially, aryl cuprates reacted cleanly with 1 to give the corresponding 4-aryl-4H-pyran with higher regioselectivity than that with alkyl cuprates. Although higher regioselectivity could be realized with RCu(I), the yield was not so good as compared with that using cuprates under the same conditions (entry 3). To our knowledge, the direct synthetic utility of 4H-pyrans had not been recognized so well.[12] Thus, we tried acid catalyzed transformation of 4H-pyrans. On treatment of 2 with a catalytic amount of conc. HCl in CH_3CN at reflux, cyclohexenone derivatives (8)[13] were formed quantitatively in one pot process (Table 2, eq.3). This was surely effected through 7, since it had been reported that 4H-pyrans easily underwent hydrolytic cleavage to 1,5-diketones with acid.[14]

Table 1. Reaction of Pyrylium Salt (1) with Organocopper Reagents

entry	copper reagent	ratio 2/3	Yield (%) 2 + 3
1	$(p\text{-tolyl})_2CuLi$	81/19$^{a)}$	90
2	$(p\text{-tolyl})_2CuMgBr$	84/16$^{b)}$	80
3	p-tolylCu(I)	89/11$^{a)}$	43
4	$(p\text{-anisyl})_2CuMgBr$	87/13$^{b)}$	93
5	$(p\text{-chlorophenyl})_2CuMgBr$	77/23$^{b)}$	77
6	$(n\text{-octyl})_2CuLi$	60/40$^{c)}$	82
7	$(n\text{-octyl})_2CuMgBr$	70/30$^{c)}$	81
8	n-octylCu(I)	71/29$^{c)}$	75
9	$(\text{phenethyl})_2CuMgBr$	70/30$^{c)}$	71

a) Calculated from yields of 2 and 6. b) Calculated from yields of 2 and 5. c) Estimated from ^1H nmr data.

Table 2. Transformation from 4H-pyrans into Cyclohexenones.

entry	R 2	React. time(h)	Yield(%) 8
1	p-tolyl	35	86
2	n-octyl	17	quant.
3	phenethyl	20	quant.

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7. Compound 2a: colorless oil; ^{1}H nmr (CDCl$_3$): δ 1.41 (3H, s), 1.80 (6H, s), 2.29 (3H, s), 4.52 (2H, s), 7.11 (2H, d, J=6.1 Hz), 7.23 (2H, d, J=6.1 Hz); ir (neat): 1710, 1155, 800 cm^{-1}; Mass: 214 (M$^+$).

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9. Compound 6a; colorless oil ; ^{1}H nmr (CDCl$_3$): a mixture of diastereomers, δ 0.86, 0.88 (3H, d, J=6.1 Hz), 1.19, 1.21 (3H, d, J=6.8 Hz), 1.30-1.90 (4H, m) 2.00, 2.04 (3H, s), 2.30 (3H, s), 2.42-2.91 (2H, m), 7.07 (4H, s); ir (neat) 1710, 1353, 807 cm^{-1}; Mass: 218 (M$^+$).

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11. Compound 5a; pale yellow oil; ^{1}H nmr (acetone-d$_6$): δ 1.55 (3H, d, J=1.3 Hz), 1.64 (3H, s), 1.84 (3H, s), 2.28 (6H, s), 2.97 (2H, s), 6.23 (1H, q, J=1.3 Hz), 6.95-7.40 (8H, m); ir (neat): 1700 cm^{-1}; Mass: 306 (M$^+$).

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13. Compound 8a; colorless oil ; ^{1}H nmr (CDCl$_3$): δ 1.33 (3H, s), 1.97 (3H, d, J=1.5 Hz), 2.29 (3H, s), 2.46 (1H, d, J=15 Hz), 2.51 (1H, d, J=15 Hz), 2.68 (1H, d, J=15 Hz), 2.78 (1H, d, J=15 Hz), 5.86 (1H, J=1.5 Hz), 7.14 (4H, s); ir (neat): 1660, 1515, 807 cm^{-1}; Mass: 214 (M$^+$).

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