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REGIOSELECTIVE ADDITION OF ORGANOCUPRATES TO 2-SILOXYPYRYLIUM SALT: FACILE SYNTHESIS OF SUBSTITUTED 2-SILOXY-4H-PYRANS AND THEIR REACTIONS WITH ELECTROPHILES

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Abstract: 2-Siloxy-4H-pyrans (3) were prepared from 2-siloxypyrylium salt (2) by the addition of organocuprates to 4-position with good regioselectivity. The product 3 reacted with some electrophiles to give the corresponding 3,4-disubstituted 3,4-dihydro-2-pyrones (6—8).

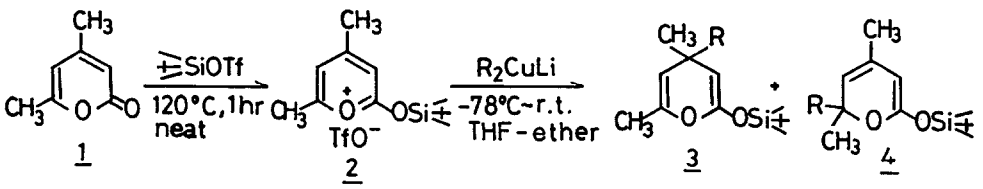
The 2-pyrone and dihydro-2-pyrone derivatives are found in various types of natural products and are important synthetic intermediates.[1] Most methods currently available for their preparations, however, involve ring closure of pre-functionalized acyclic systems,[2] hence it is desirable to device some general methods for introduction of substituents into the pyrone rings. Toward this end we report here the regioselective synthesis of 2-siloxy-4H-pyrans (3) from 2-pyrone (1) via 2-siloxypyrylium salt (2), and in addition the potential utility of 3 to prepare some 3,4-disubstituted 3,4-dihydro-2-pyrones (6—8). This method is attractive in the following points: (i) several organocuprates added to the 4,6-dimethyl-2-siloxypyrylium salt (2) prepared in situ from silyl triflate and 4,6-dimethyl-2-pyrone (1), which was unreactive toward the organocuprates,[3] (ii) we could obtain the adducts (3) in the form of reactive ketene silyl acetals, which have been well demonstrated to undergo various electrophilic attack.[4]

The 2-siloxypyrylium salt (2) could be prepared by mixing 4,6-dimethyl-2-pyrone (1) with tert-butyldimethylsilyl triflate without solvent and heating the mixture to 120 °C for 1 h. Formation of 2 could be detected by ^{1}H-NMR spectrum (CD_3CN), in which all the protons of the ring moved downfield by approximately 1 ppm as a result of the silylation (δ 5.87 and 5.94 in 1 vs δ 6.62 and 6.84 in 2). This shift is comparable to that of 2-methoxypyrylium salt prepared by the reaction of 1 with trimethyloxonium salt.[5] The salt 2 was unstable to atmospheric moisture, therefore it was used in situ for the following reactions with organocuprates. A typical experimental procedure was as follows. To a suspension of 2 (12.0 mmol) in ether (24 ml) was added a THF solution (25 ml) of cuprate (14.4 mmol) at -78 °C under nitrogen atmosphere with stirring and the reaction mixture was warmed to room temperature and then poured onto ice-cooled 5% aq Na_2CO_3 (150 ml), and the mixture was filtered through celite. The resulting filtrate was extracted with ether (75 ml x 2) and organic layers were combined, dried over molecular sieves 4A under nitrogen atmosphere, evaporated to give the crude product. Short column chromatography of the crude product on Al_2O_3 (basic, n-hexane: AcOEt=19:1 as an eluent) afforded 4-substituted 4,6-dimethyl-2-t-butyldimethylsiloxy-4H-pyrans (3). The treatment with alumina should be done as quickly as possible, otherwise the hydrolyzed product (5), the corresponding lactone, would be obtained. The

results of the reaction of 2 with several cupartes are summarized in Table 1. The cuprates from lithium reagents reacted more effectively than those from Grignard reagents (entry 10 and 11), and in addition in the reaction with alkylcuprates from Grignard reagents we obtained the products (5) in the hydrolyzed form (entry 11). Concerning the regioselectivity, aryl, alkenyl and secondary alkyl cuprates reacted exclusively at 4 position to give 3[6] in moderate yields (entry 1 – 5), while primary alkyl and methyl cuprates yielded a mixture of 3 and 4[7] (entry 6 — 9). Although the ratio of the mixture in the reaction with these cuprates were sensitive to solvents, these results on the regioselectivity were related to those of the reactions of 2,4,6-trimethylpyrylium tetrafluoroborate with various cuprates,[8] suggesting that this reaction proceeded through 2-siloxypyrylium salt (2).

In order to investigate the synthetic utility of 3, various electrophiles were reacted with 3 (scheme 2). On treating with N-bromosuccinimide (NBS) in DMF solution at -30 — 0 °C,[4b] 3-bromo-3,4-dihydro-2-pyrone derivatives (6) were obtained in good yields as a mixture

Scheme1



R: a) p-$CH_3C_6H_4$-, b) CH_2=CH-, c) CH_3CH=CH-, d) CH_2=C(CH_3)-, e) sec-butyl, f) n-butyl, g) methyl, h) i-propyl.

Table 1. Reaction of 2-Siloxypyrylium Salt 2 with R_2CuLi.

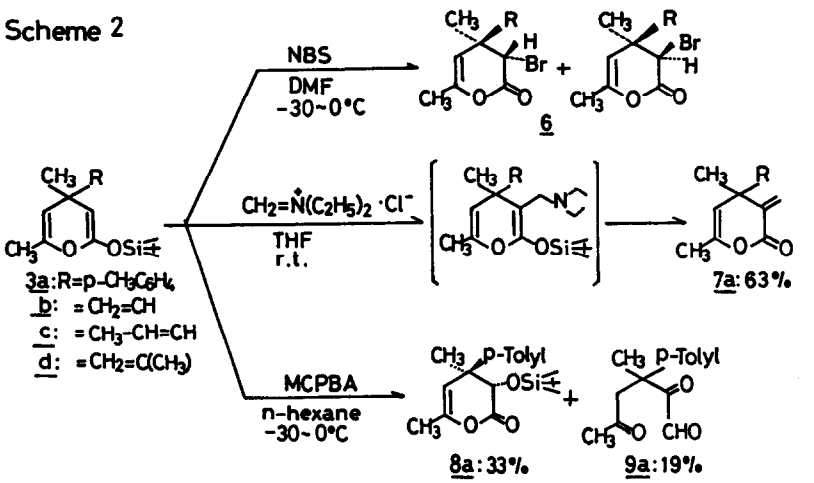
Entry	R_2CuLi (1.2 eq)	Solvent	Product	Isolated Yield (%)	Ratio of 3 / 4
1.	[p-$CH_3C_6H_4$-]$_2$CuLi	THF-ether	3a	65	100/0
2.	[CH_2=CH-]$_2$CuLi	THF-ether	3b	44	100/0
3.	[CH_3CH=CH-]$_2$CuLi[b]	THF-ether	3c	52[b]	100/0
4.	[CH_2=C(CH_3)-]$_2$CuLi	THF-ether	3d	42	100/0
5.	sec-butyl$_2$CuLi	ether-cyclohexane	3e	43	100/0
6.	n-butyl$_2$CuLi	ether-n-hexane	3f+4f	65	57/43[a]
7.	"	ether-THF-n-hexane	"	70	40/60[a]
8.	methyl$_2$CuLi	THF-ether	3g+4g	53	38/62[a]
9.	"	ether	"	c)	0/100[a]
10.	[p-$CH_3C_6H_4$-]$_2$CuMgBr	THF-ether	3a	28	100/0
11.	i-propyl$_2$CuMgBr	THF-ether	5h	42	100/0

a) Estimated from ^{1}H-NMR data. b) Cis, trans mixture. c) Not determined.

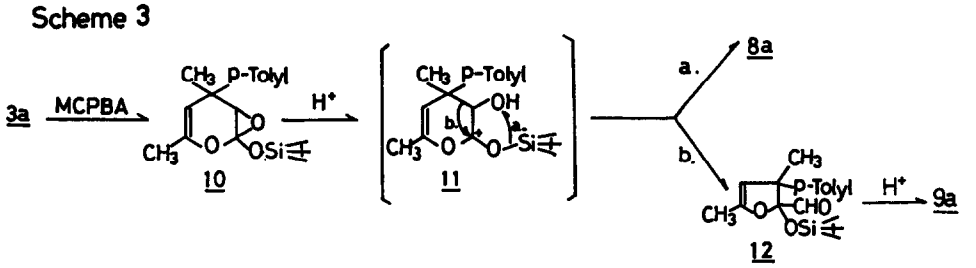
of diastereomers. The results are shown in Table 2. We did not determine the exact structure of the two diastereomers, but interestingly during the purification process with TLC (silica gel) isomerization took place between the isomers to result in the predominant formation of one diastereomer.[9] Reaction of 3 with an iminium salt[10] at room temperature followed by treatment with TLC (silica gel) directly yielded α-methylene—δ-lactones (7)[11] in moderate yields. In general cases, similar conversions from the Mannich base to such α-methylene carbonyl compounds are not so easy, two steps are usually required for the completion, i.e., (i) quaternization of the Mannich base, (ii) deamination from the resulting quaternary salt with base.[4c] It is not unreasonable to presume that in this case, the steric crowding at C_3 of the resulting Mannich base facilitates the elimination of the amino group during TLC separation. This reaction provides a facile and new route to α-methylene-δ-lactone derivatives which have been difficult to be prepared and interested in their potential biological activities.[12]

Next, we examined the reaction of 3 with peracid.[4d] Oxidation of 3a with MCPBA in n-hexane suspension at -50 - 0 °C afforded the crystalline α-siloxy-δ-lactone (8a)[13] as a single diastereoisomer (33 %) together with α,δ-diketoaldehyde (9a) (19 %) after TLC (silica gel) separation. The possible mechanism for the formation of these compounds 8a and 9a can be described as shown in scheme 3. The initial formation of the epoxide 10 was followed by ring opening to dioxacarbenium ion 11 with proton. The 1,4-silyl rearrangement should give the α-siloxy-δ-lactone (8a), but if the rate of this rearrangement was slow due to steric crowding, skeletal rearrangement would compete with the silyl rearrangement to give 12 and finally the ring-opened 9 could be produced.[14]

Scheme 2



Scheme 3



In summary 2-siloxy-4H-pyrans (3) were obtained by the reaction of 2-siloxypyrylium salt (2) with cuprates and were found to be useful for further transformation. We are currently investigating the potentiality of 3 in the synthesis of valuable 2-pyrone derivatives.

Table 2. Reaction of 3 with NBS in DMF.

Entry	R	Isolated Yield (%)	Ratio[a] Major/Minor
1.	p-$CH_3C_6H_4$-	75	94/6
2.	CH_2=CH-	47	88/12
3.	CH_3CH=CH-	72	b)
4.	CH_2=C(CH_3)-	57	88/12
5.	methyl	37	-

a) Estimated from ^{1}H-NMR data after purification with silica gel column chromatography. b) The ratio could not be determined from the ^{1}H-NMR data.

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(6) 3a: ^{1}H-NMR (CD_3COCD_3) δ 0.21 (s, 6H), 0.97 (s, 9H), 1.44 (s, 3H), 1.80 (d, 3H, J=1.1Hz), 2.25 (s, 3H), 3.96 (d, 1H, J=2.2Hz), 4.51-4.67 (m, 1H), 7.07 (d, 2H, J=8.1Hz), 7.23 (d, 2H, J=8.1Hz).

(7) 4g: ^{1}H-NMR (CD_3COCD_3) δ 0.28 (s, 6H), 0.95 (s, 9H), 1.83 (brs, 6H), 2.20 (d, 3H, J=1.1Hz), 5.64 (brs, 1H), 5.67-5.84 (m, 1H).

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(9) 6a (major isomer, assigned as trans): ^{1}H-NMR ($CDCl_3$) δ 1.59 (s, 3H), 2.06 (d, 3H, J=1.3Hz), 2.31 (s, 3H), 4.61 (d, 1H, J=1.5Hz), 4.92-5.06 (m, 1H), 6.97-7.31 (m, 4H). 6a (minor isomer, assigned as cis): ^{1}H-NMR ($CDCl_3$) δ 1.58 (s, 3H), 2.03 (d, 3H, J=1.1Hz), 2.33 (s, 3H), 4.55 (d, 1H, J=1.1Hz), 5.30-5.42 (m, 1H), 6.95-7.30 (m, 4H).

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(11) 7a: ^{1}H-NMR ($CDCl_3$) δ 1.49 (d, 3H, J=0.9Hz), 1.84 (brs, 3H), 2.22 (s, 3H), 5.00 (brs, 1H), 5.46 (brs, 1H), 6.35 (brs, 1H), 7.04-7.25 (m, 4H).

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(13) 8a: ^{1}H-NMR ($CDCl_3$) δ -0.47 (s, 3H), -0.05 (s, 3H), 0.72 (s, 9H), 1.43 (s, 3H), 1.94 (d, 3H, J=1.1Hz), 2.32 (s, 3H), 4.33 (s, 1H), 5.05 (brs, 1H), 7.12 (d, 2H, J=8.8Hz), 7.21 (d, 2H, J=8.8Hz). 9a: ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H), 2.01 (s, 3H), 2.32 (s, 3H), 3.08 (brs, 2H), 7.15 (s, 4H), 9.51 (s, 1H).

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