FACILE ROUTE TO 2,3-DISUBSTITUTED CHROMANONES VIA

CHROMONE-3-CARBOXALDEHYDE ACTIVATED BY SILYLATION

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Abstract- Aldol type condensation of chromone-3-carboxaldehyde (1) with active

methylenes in the presence of t-butyldimethylsilyl triflate afforded silylated

aldol adducts (4), which were further converted to 2,3-disubstituted chromanones by

reaction with enol silyl ethers via the corresponding 4-siloxypyrylium salts.

Functionalized chromones have attracted continuous interest due to their pharmaceutical

activity.[1] Nohara et al. reported the antianaphylactic activity for the E-β-(4-oxo-1-benzo-

pyran-3-yl)acrylic acid (5f:R^1=R^2=H),[2] which was prepared from chromone-3-carboxaldehyde (1) and

malonic acid. Aldol condensation of 1 has been used for limited substrates such as aryl methyl

ketones[4] and other highly acidic active methylenes.[1,2,3,5,6] Furthermore these methods did not

give aldol type adducts (4) but only the dehydrated α,β-unsaturated carbonyl compounds (5). We

now report the aldol type condensation of 1 to afford 4 via 4-t-butyldimethylsiloxy-

3-formyl-1-benzopyrylium triflate (2) and the conversion of 4 to 2,3-disubstituted chromanones

(6), which could not be prepared from 5.

According to the method reported recently by us,[7] chromone-3-carboxaldehyde (1) and 1 eq of

t-butyldimethylsilyl triflate were mixed without solvent and heated to 160 °C for 30 min under

nitrogen and the mixture was dissolved in CDCl$_3$ or CD$_3$CN. In the ^{1}H nmr, a ring proton at C-2

and a formyl proton of 1 (δ 8.6 and 10.4) shifted to much lower field (δ 9.6 and 15.0) and the

chemical shifts changed neither by dilution with the solvent nor by addition of excess

silylating reagent, which indicates that the covalent bonding was formed to afford a cation 2 or

3 (here we prefer 2) (Scheme 1). A reaction of 2 with enol silyl ethers took place very

quickly, the reaction completed in a few minutes even at -78 °C. But the yield of the adduct

(4) was unsatisfactory as shown in Table 1 (Scheme 2: Method A).[8] Therefore, we investigated

other conditions for the aldol type condensation and found that the following two methods could

be used instead of Method A: First, Method B (reaction of 1 with excess of an ester in the

presence of 2 eq of triflate and 1.3-2.2 eq of 2,6-lutidine in dichloromethane under reflux) was useful for the preparation of 4d and 4e with ethyl acetate and ethyl propionate. This method afforded no adducts with methyl isobutyrate, and gave 4d and 4e in high yields (Table 2). In addition either 4 or 5 could be prepared selectively by the choice of the amount of 2,6-lutidine. Under acidic (with 1.0-1.3 eq of lutidine) or basic (with 3.0 eq of lutidine) conditions, desilanol of 4 took place to give 5 as major product. On the other hand, the adduct (4) was obtained under neutral conditions (with 2.0-2.2 eq of lutidine)(Table 2). Compound 5d was hydrolyzed to give 5f (R^1=R^2=H in scheme 3)[2] in 98 % yield with 1.6 M H_2SO_4 under reflux for 1.5 h. As with aliphatic ketones the system gave a complex mixture, and Method C (premixing of a ketone with 1 eq of silyl triflate and 1 eq of 2,6-lutidine at room temperature and the mixture was added to the pyrylium salt in the presence of 1.2 eq of 2,6-lutidine) was developed for aliphatic ketones. For example, 4a was obtained in 84 % yield by Method C. For alkyl aryl ketones Methods B and C gave only the corresponding desiloxylated compound (5) in 89-94 % yield.
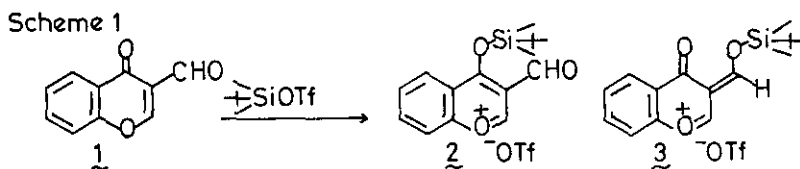
Scheme 1

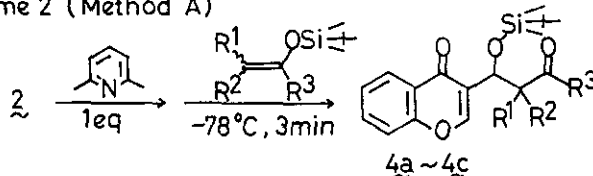Scheme 2 (Method A)

Table 1   Yield of 4a-4c by Method A [a]

Entry	Product 4	R^1	R^2	R^3	Yield (%)
1	4a	H	H	i-Pr	36
2	4b	Me	Me	Me	40
3	4c	Me	Me	OMe	50

a) see text

Scheme 3 (Method B)

4d : R¹=H, R²=Et   5d : R¹=H, R²=Et
4e : R¹=Me, R²=Et   5e : R¹=Me, R²=Et
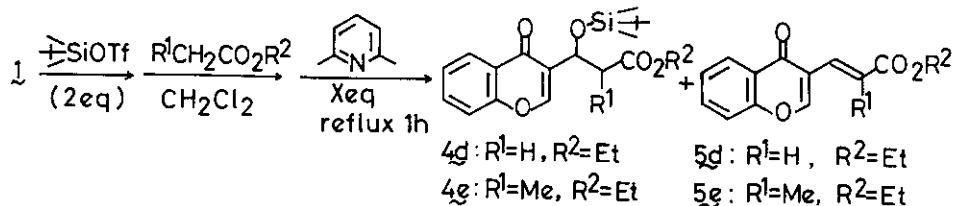
Table 2   The Effect of the Amount of 2,6-Lutidine on the Product (Method B)

Entry	R^1	R^2	2,6-lutidine X(eq)	Yield (%) 4	Yield (%) 5
1	H	Et	0.5	0	0
2			1	0	50
3			1.3	0	80-92
4			1.7	40	50
5			2.0	89	8
6			2.2	96	0
7			3.0	0	90
8	Me	Et	1.5	4	82
9			2.0	92	6

Scheme 4 (Method C)

4a   84%
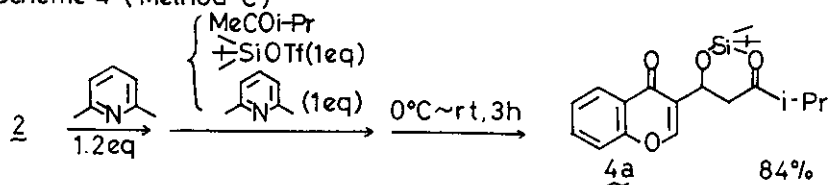
Scheme 5
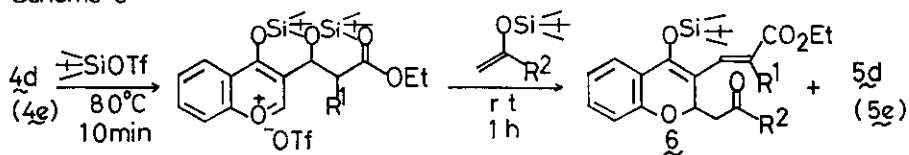
Table 3   Synthesis of 2,3-Disubstituted Chromanones (6)

Entry	R^1	R^2	temp	Product 6	Yield (%) 6	Yield (%) 5
1	H	i-Pr	rt	6a	72	23
2			0°C		63	37
3	H	OMe	rt	6b	74	18
4	Me	i-Pr	rt	6c	62	29

In order to introduce a second group into the ring, the adducts 4 and 5 were silylated again to form the corresponding pyrylium salts, which were subjected to react with enol silyl ethers or active methylene compounds. Although 5 gave a complex mixture, 4 afforded the expected 2,3-disubstituted chromanones (6) with concomittant formation of 5. The yields of 6 and 5 varied by the reaction conditions and are summarized in Table 3.

In summary the aldol type adduct (4) thus obtained could be used as precursor for the preparation of 2,3-disubstituted chromanones (6), hence we presented a unique and facile method for functionalization of chromones.

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8. Compound 4d; ^{1}H nmr (CDCl$_3$) δ 0.03 (6H, s), 0.94 (9H, s), 1.26 (3H, t, J=7 Hz), 2.61 (1H, dd, J=14.5, 7.0 Hz), 2.91 (1H, dd, J=14.5, 4.0 Hz), 4.20 (2H, q, J=7 Hz), 5.40 (1H, ddd, J=1.1, 4.0, 7.0 Hz), 7.18-7.67 (3H, m), 7.90 (1H, d, J=1.1 Hz), 8.14 (1H, dd, J=0.9, 7.4 Hz); Mass: 376 (M$^+$).

9. Compound 5d; ^{1}H nmr (CDCl$_3$) δ 1.33 (3H, t, J=7.0 Hz), 4.26 (2H, q, J=7 Hz), 7.21 (1H, d, J=13.2 Hz), 7.21-7.80 (3H, m), 7.57 (1H, d, J=13.2 Hz), 8.11 (1H, s), 8.25 (1H, dd, J=0.9, 6.6 Hz); Mass: 244 (M$^+$).

10. Compound 6a; ^{1}H nmr (CDCl$_3$) δ 0.00 (6H, s), 0.86 (9H, s), 1.09 (6H, d, J=6.8 Hz), 1.32 (3H, t, J=6.2 Hz), 2.27 (1H, dd, J=16.4, 2.2 Hz), 2.52 (1H, sep, J=6.8 Hz), 3.12 (1H, dd, J=16.4, 10.1 Hz), 4.21 (1H, q, J=6.2 Hz), 5.71 (1H, d, J=16.3 Hz), 5.76 (1H, dd, J=10.1, 2.2 Hz), 6.74-7.45 (4H, m), 7.79 (1H, d, J=16.3 Hz); Mass: 432 (M$^+$).

11. Other products described in the text gave satisfactory nmr and ms data, and 4d, 5d, and 6a gave correct elemental analyses.

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