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t-BUTYL LITHIOACETATE ON ORTHO-HYDROXYPHENONES PROVIDING 2-METHYLCHROMONES. AN EASY ACCESS TO KHELLIN[1]

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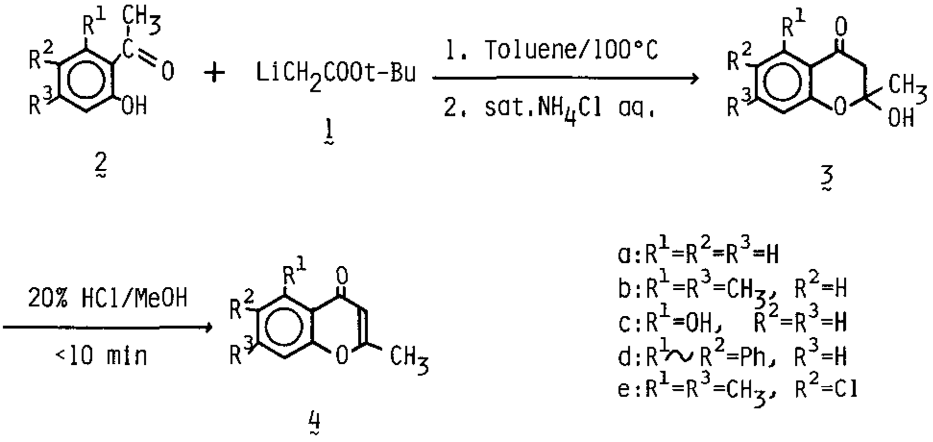
Abstract——Reaction of t-butyl lithioacetate with several kinds of poly-substituted ortho-hydroxyphenones including khellinone and subsequent acid-hydrolysis of the resulting hemiacetals provide the corresponding 2-methylchromone derivatives in excellent overall yields.

Benzo-γ-pyrones, known as chromones are the parent of a great number of naturally occurring compounds and in recent years many kinds of 2-methylchromones have been successively isolated from plants[2] and fungal metabolites[3], some of which possessing an eligible biological activity.[4] Three representatives have been widely known for the synthesis of chromones starting from multi-substituted ortho-hydroxyphenones, *viz.*, the Claisen condensation[5], the Baker-Venkataraman reaction[6] and the Kostanecki reaction.[7] In every case, however, there have been some critical shortcomings whatsoever. In the first case, reactions often undergo, for instance, in low yield due to competing side reactions involving mainly self-condensation of the starting phenone and/or the ester employed, markedly when phenone has the bulky substituents around carbonyl and *ethyl acetate* would be used. The Baker-Venkataraman synthesis usually gives 2-alkylchromones in only a marginal yield and is not the method of choice for this purpose. An extremely hard-to-separate mixture of chromones and coumarins would be sometimes furnished in the last and the drastic reaction conditions commonly operated would not be compatible with sensitive functionality.

As part of our continuing effort on the utility of t-butyl lithioacetate[1,8], particularly as a noticeable two-carbon homologation agent, we have disclosed in this letter that reaction of this promising reagent with several kinds of poly-substituted ortho-hydroxyphenones led to the otherwise inaccessible chromanone hemiacetals, 3 isolated at first without any difficulties, and then to 2-methylchromones, 4 as final products after acid-hydrolysis in high overall yields.



a: $R^1=R^2=R^3=H$
b: $R^1=R^3=CH_3$, $R^2=H$
c: $R^1=OH$, $R^2=R^3=H$
d: $R^1 \sim R^2=Ph$, $R^3=H$
e: $R^1=R^3=CH_3$, $R^2=Cl$

Table 1. Physical Data for Chromanone Hemiacetals, 3_{a-e}

	3_a	3_b[a]	3_c[a]	3_d[a]	3_e
Isolated Yield(%)	90	86	90	87	85
Appearance (colorless cryst.) mp(°C)	semisolid	needles 118-119 (Hexane)	needles 125 (EtOH)	prisms 164-165 ($CHCl_3$)	semisolid
MS m/z(M^+)	178	192	194	228	240/242=3
IR $\nu_{cm^{-1}}^{nujol}$ for -OH	3400	3300	3300	3430	3350
for >C=O	1650	1660, 1620	1650, 1610	1650, 1610	1660, 1630
PMR $\delta_{ppm}^{CDCl_3}$ for -OH	4.1[b]	4.0[b]	4.0[b] (10.5)	3.9[b,c]	4.0[b]
CMR $\delta_{ppm}^{CDCl_3}$ for >C=O	190.50	193.10	190.35	193.15[c]	189.50

a) Satisfactory microanalyses were obtained(C ±0.25%, H ±0.13%).

b) Disappearance on addition of D_2O. c) Taken in DMSO-d_6.

The following comments which should be pointed out have appeared. Firstly, yields are always high in every step even in case of the phenones bearing the bulky substituents(2_d and 2_e); no formation of an inseparable mixture with undesired coumarins was observed. Secondly, chromanone hemiacetals, 3_{a-e} are isolated and fully

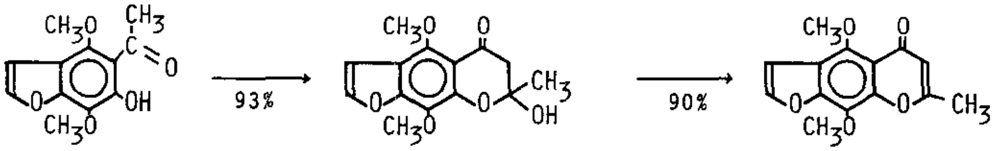
Table II. Physical Data for 2-Methylchromones, **4**a-e

	4a	**4**b	**4**c	**4**d	**4**e
Isolated Yield(%)	95	98	93	95	90
Appearance (colorless cryst.)	needles	needles	needles	prisms	plates
mp(°C)	72-73	55-56	90-91	171-171.5[a)]	144-145
Lit. mp(°C)	71[9]	55-56[10]	92[11]	164[10]	145-146[12]
MS m/z(M^+)	160	174	176	210	222/224=3
CMR $\delta_{ppm}^{DMSO-d_6}$ for >C=O	175.50	178.59	177.85	178.83	176.67

a) Sublimed at 100°C/2 Torr for 30 min and then recrystallized from ethanol. Satisfactory microanalysis was also obtained.

characterized which being only postulated as most likely intermediates before. Lastly, all of the starting phenones are readily available from the corresponding phenyl acetates *via* the Fries rearrangement.

Likewise, this procedure proved to be efficiently applicable to the preparation of khellin[2,13], which is one of the well-known constituents of *Ammi visnaga L.*, exhibiting strongly desirable lipid-altering activity demonstrated recently by Gammill *et al.*[4]



Khellinone
commercially
accessible

7-Hydroxydihydrokhellin
a slightly yellow powder
mp 103.5-104.5°C
m/z(M^+) 278
$\nu_{cm^{-1}}^{KBr}$ for -O$\underline{H}$ 3525, for >$\underline{C=O}$ 1630,1610
$\delta_{ppm}^{CDCl_3}$ for -O$\underline{H}$ 4.3, for >$\underline{C}$=O 194.56

Khellin
mp 153-155°C
(Lit.[2,13] mp 154-155°C)
m/z(M^+) 260
$\delta_{ppm}^{CDCl_3}$ for >$\underline{C}$=O 178.25

In conclusion, although being regarded as a kind of a Claisen condensation according to the intermediates obtained, the synthesis of 2-methylchromones described here by using t-butyl lithioacetate is operationally simple and gives high yields of the products and thus appears to offer a valuable alternative effecting such transformations.

A general procedure is as follows: 1) Under an argon atmosphere, solid t-butyl lithioacetate[8](15.0g, 124mmol, 5eq. to 2_a) was added in three portions at 100°C with vigorous stirring to a solution of compound, 2_a(3.4g, 25mmol) in dry toluene (200ml) freshly distilled from benzophenone ketyl. After 2 h, quenching the reaction with sat.NH_4Cl aq.(100ml) under cooling followed by a usual work-up gave an oily solid. Careful trituration of the resulting residue with cold n-pentane produced a semisolid(3_a, 4.0g, 90%). 2) A mixture of the hemiacetal(3_a, 4.0g, 22.5 mmol), 20% HCl aq.(10ml) and methanol(20ml) was heated at 80°C(bath temp.) with stirring. After 10 min, evaporation of the reaction mixture under reduced pressure at 10°C furnished a slightly yellow semisolid which was recrystallized from n-hexane to yield 2-methylchromone as colorless needles(4_a, 3.4g, 95%), mp 72-73°C.

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