A CERIUM METAL-MEDIATED COUMARIN SYNTHESIS[1,2]

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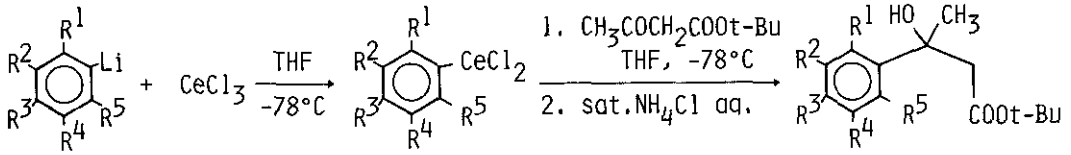
Abstract—— Chemoselective carbonyl 1,2-addition of organocerium reagent derived from polysubstituted phenyllithium and cerium(III) chloride to t-butyl acetoacetate and the succeeding acid-treatment furnish the substituted 4-methylcoumarins in reasonable yields.

Coumarins are widespread in nature and have been reported to possess the various biological and/or pharmacological properties.[3] As for their synthesis, however, some coumarins expected are not always acquired exclusively. From biological and synthetic standpoints, much efforts have been still devoted to exploring new syntheses of this class of compounds, notwithstanding many known representative procedures.[4]

In the past, a great deal of research on the organocerium chemistry was carried out perseveringly by Imamoto et al. and by others.[5] In our previous report[6], we also revealed that a novel organocerium reagent, $Cl_2CeCH_2COOt\text{-}Bu$, reacted efficiently with the easily enolizable substituted acetophenones to produce the desired 1,2-adducts in high yields. On the other hand, attempt of an organocerium reagent on β-keto esters like alkyl acetoacetates has appeared not to be performed so far.

As an extension of our exploitation of a widely applicable method to the biologically active coumarin synthesis, therefore, we turned our attention toward the reaction of phenylcerium(III) chloride with t-butyl acetoacetate and examined the right one strenuously in order to find out the optimum reaction conditions.

As a result, reaction of 2 eq. of phenylcerium(III) chloride, 2a, with t-butyl acetoacetate proceeded cleanly at -78°C to afford an 81% optimum yield of the 1,2-carbonyl adduct accompanying with (16%) t-butyl acetoacetate intact, which was in good agreement with the keto/enol ratio of the ester determined by ^1H nmr in tetrahydrofuran-d_8. With this experimentation, the readily available compounds, 1b-f,



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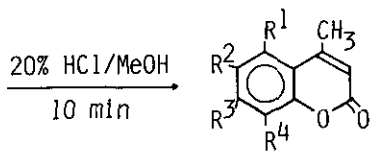

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a: $R^1=R^2=R^3=R^4=R^5=H$
b: $R^1=R^2=R^3=R^4=H$, $R^5=OMOM$
c: $R^1=R^3=CH_3$, $R^2=Br$, $R^4=H$, $R^5=OMOM$
d: $R^1=R^2=-(CH=CH)_2-$, $R^3=R^4=H$, $R^5=OMOM$
e: $R^1=R^3=CH_3$, $R^2=R^4=Cl$, $R^5=OMOM$
f: $R^1=R^2=R^3=Cl$, $R^4=H$, $R^5=OMOM$
(OMOM=OCH_2OCH_3)

Table Physical Data for 4-Methylcoumarins, 4_{b-f}

	4_b	4_c[a]	4_d	4_e[a]	4_f[a]
Isolated Yield(%)[b]	75	78	78	70	73
Appearance (colorless cryst.)	plates	prisms	needles	needles	needles
mp(°C, aq.EtOH)	82.5-83.5[c]	201.5-202.5	180.5-181	214.5-215	216-217
Lit. mp(°C)	83-84[8]		182-183[9]		
MS m/z(M^+)	160	266/268=1	210	256/258/260=9/6/1	262/264/266/268=27/27/9/1
CMR $\delta_{ppm}^{DMSO-d_6}$ for >C=O	160.63	159.93	173.55	158.81	158.28

a) Satisfactory microanalyses were obtained(C ±0.15%, H ±0.08%).

b) Based on t-butyl acetoacetate.

c) Sublimed at 50°C/2 Torr for 30 min and then recrystallized from aq.EtOH.

delineated in the scheme emerged as starting materials. Compounds, 1_{b-f}, were obtained in high yields from the corresponding commercially available phenols which were first brominated and then methoxymethylated with KH/$ClCH_2OCH_3$ in THF followed by lithiation with n-BuLi. Thus, addition of the substituted phenylcerium(III) reagents, 2_{b-f}, to t-butyl acetoacetate took place under similar and well-controlled reaction conditions and the subsequent acid-hydrolysis of all the 1,2-adducts, 3_{b-f}, although being purified by silica gel chromatography if required, furnished directly the expected coumarins, 4_{b-f}[7], without any problems.

In conclusion, the ready availability of both the starting materials and the simple

manipulation make this coumarin synthesis presented a beneficial alternative to the existing methods. Even more noteworthy, this informed method may open an application to the synthesis of the otherwise inaccessible and biologically valuable coumarins substituted at the 3 or 4 position or at both the 3 and 4 positions.

The following is typical: Under an argon atmosphere at -78°C, the milky fine suspension of $CeCl_3$(1.1 g, 4.5 mmol, 2.25 eq. to the ester) in dry THF(9 ml) freshly distilled from benzophenone ketyl was added dropwise by using a pressure equalizing dropping funnel with a Dewar condenser to the THF solution of phenyllithium($\underset{\sim}{1}_b$, 2 eq. to the ester) which had been prepared from ortho-methoxymethoxybromobenzene and n-BuLi in dry THF at -78°C and the whole was stirred for 1 h to produce an orange yellow solution of $\underset{\sim}{2}_b$. Then, to this was added at the same temperature t-butyl acetoacetate(316 mg, 2 mmol) in dry THF(1 ml) via a squirt and the resulting mixture was stirred for an additional 3 h. Centrifuged separation and evaporation of an organic layer after quenching the reaction with sat. NH_4Cl aq.(20 ml) gave a light yellow oil containing $\underset{\sim}{3}_b$, which was submitted to heating at 80°C for 10 min in a mixture of 20% HCl aq.(1 ml) and MeOH(3 ml). Concentration to dryness below 50°C under vacuo and washing the resulting oily semisolid once with cold 10% NaOH aq. (3 ml) afforded a white solid. Sublimation at 50°C/2 Torr for 30 min followed by recrystallization from aq. EtOH yielded 4-methylcoumarin as colorless plates($\underset{\sim}{4}_b$, 240 mg, 75%), mp 82.5-83.5°C.

REFERENCES AND NOTES

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