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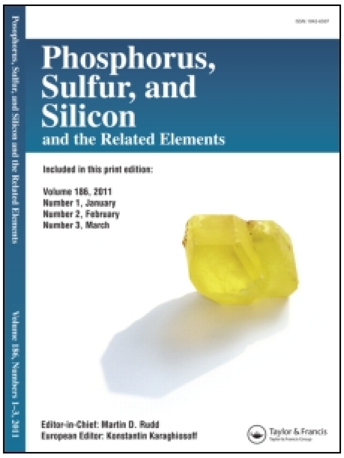

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Evaluation of TCS/ZnCl$_2$ with Acetic Anhydride as an Acetylating Reagent for Methylene Ketones

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A new route for the preparation of β-diketones which have applications in organic synthesis by the reaction of methylene ketones, acetic anhydride, TCS and ZnCl$_2$ in the solvent methylene chloride at room temperature produces the corresponding β-diketones in excellent yield.

Keywords (TCS) tetrachlorosilane

Many newer methods involving the use of ingeniously designed coupling reagents have been discovered.[1–4] The acylation of methylene ketones to form β-diketones could be affected with acid anhydride by means of acids[5,6] or bases.[7,8]

The reaction of silicon anhydrides of monobasic organic acids with acetylene, it has been reported that,[9] in presence of aluminum chloride as catalyst yielded alkyl β-chlorovinyl ketone as shown in Scheme 1.

$$\mathrm{(RCOO)_4Si + C_2H_2 \longrightarrow (RCOCH{=}CH\text{-}O)_4Si}$$

$$\mathrm{(RCOCH{=}CH\text{-}O)_4Si + AlCl_3 \longrightarrow RCOCH{=}CHCl + Si(OAlCl_2)_4}$$

SCHEME 1

In the presence of Lewis acids[5] such as boron trifluoride the acylation of methylene ketones by acetic anhydride gave a mixture from C-acetyl and O-acetyl derivatives. Trialkylsilyl enol ethers were acylated with acetyl tetrafluoroborate in nitromethane as solvent. This method[10] gave 1,3-diketone, other methods for the acylation of

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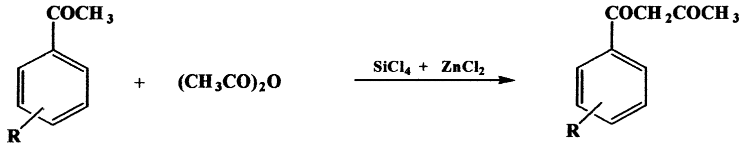
trialkylsilyl enol ethers gave exclusive O-acylation,[11] or was restricted to polyhalogenated acid chlorides.[12]

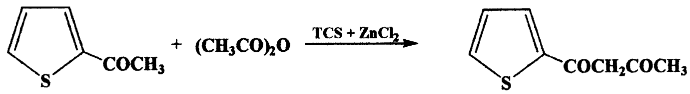
Preliminary experiments indicated that the reaction of carbonyl compounds having α-hydrogen atoms with acetic anhydride in presence of tetrachlorosilane (TCS) did not yield the desired product while the starting material could be recovered.

Our task was therefore to identify as chemoselective reactions. Because of the ready availability of TCS and its apparent efficiency in mediating the formation of the acyloxysilane, the employment of a catalytic amount of Lewis base or acid in the reaction of ketone with acetoxysilane gave better but still unsatisfactory results. After many unsuccessful trials, it was found that zinc chloride and TCS in molar ratio were efficient as a binary reagent for the synthesis of β-diketones.



(1)

We have extended our investigation to the use of TCS/ZnCl$_2$ as a coupling reagent for the synthesis of different diketones. By this method, varieties of substituted diketones are prepared in quantitative yields.

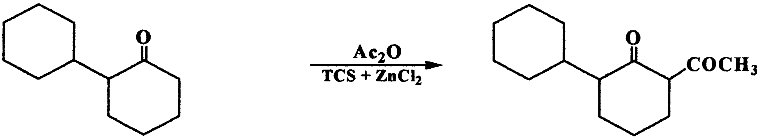


(7)

(2)

It has been reported[10] that the reaction of acetyl chloride with cyclohexanone trimethyl enol ethers in the presence of TCS gave a trace of C-acylated product, while in the presence of ZnCl$_2$ gave 63% of C-acetylated and 3% of O-acetylated products and approximately 20% from starting material were obtained. In a one step reaction the acetylation of cyclohexanone by acetic anhydride with TCS/ZnCl$_2$ as a binary reagent provided 2-acetylcyclohexanone (8) in 86% yield. The potential by product 1-acetoxycyclohexene, was not detected even in the presence of the excess reagent. It is interesting to note that 2-acety-4-*t*-butylcyclohexanone (9) also was selectively obtained from the reaction of 4-*t*-butylcyclohexanone with acetic anhydride. The products were purified by TLC chromatography and fully characterized by IR, NMR, and mass spectra (experimental section).

In view of the selectivity of TCS/$ZnCl_2$ reagent toward carbonyl compounds, especially hindered ketones, it was of interest to investigate the reaction of 2-cyclohexylcyclohexanone. Thus, we attempted the introduction of an acetyl substituent in 2-cyclohexylcyclohexanone. By refluxing the reaction mixture for 10 hours 2-acetyl-6-cyclohexylcyclohexanone (10) formed preferentially due to steric hindrance at the original 2-cyclohexyl position.



(10)

(3)

We have achieved considerable success with this procedure and the results for a variety of ketones containing α-hydrogen atoms are reported in the following table.

It was found that the reaction of β-keto-esters containing a high percentage of enol with TCS/Ac_2O in the presence of Lewis base[13] such as triethylamine yielded O-acetyl derivatives in low yield. When ethyl succinosuccinate was applied to the reaction, under the same conditions as in Table I, the starting material was recovered, since no O-acetylation occurred.

The addition of methylene chloride as solvent as well as allowing the reaction mixture to stir at room temperature significantly increased the yield of 1,3-diketone from the reaction with TCS/$ZnCl_2$ reagent.

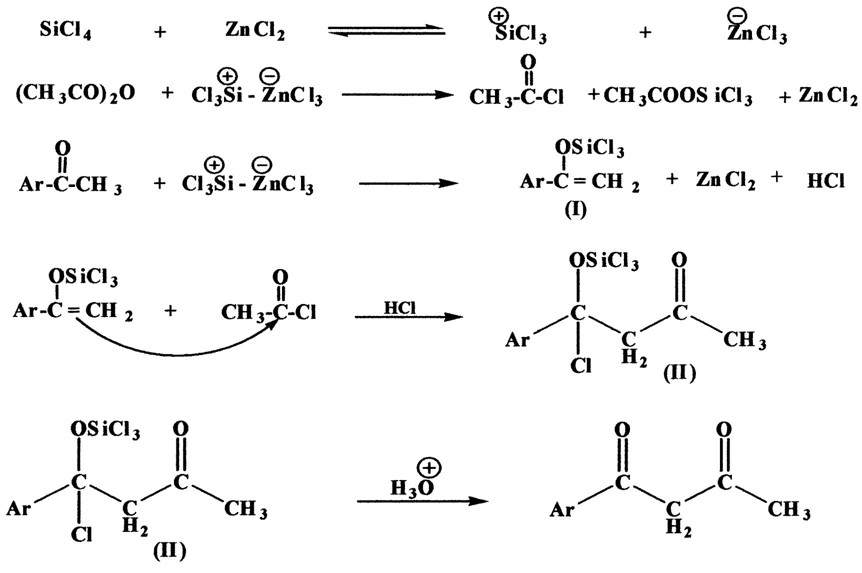
It is important to consider that, the butanedione derivative as product was obtained after the hydrolysis of the reaction mixture. The divalent zinc is able to accept halogen ion from silyl halide to generate a $\mathbf{Cl_3Si^+\text{-}\bar{Z}nCl_3}$ like species and that such species should be applicable for the activation of electrophiles, as promoters, in various reactions with moderately reactive silyl nucleophiles.[14]

A mechanistic explanation of the acetylation would involve initial formation of trichlorosilyl acetate ($AcOSiCl_3$) and no hydrochloric acid present in the first step as reported in the other methods.[10–12] An important point to consider the probable formation of acetyl chloride, as a sequence of the addition of the starting materials, may be from the reaction of $\mathbf{Cl_3Si^+\text{-}\bar{Z}nCl_3}$ with acetic anhydride. The silyl enol ether as intermediate (I) is formed from reaction of ketone with $\mathbf{Cl_3Si^+\text{-}\bar{Z}nCl_3}$

TABLE I Evaluation of TCS/$ZnCl_2$ with Acetic Anhydride as an Acetylating Reagent for Methylene Ketones

Exp. no.	Substrate	Time (hr)	Product	Yield (%)
1	Acetophenone	5	1-phenyl -1,3-butanedione (1)	86
2	4′-Methylacetophenone	4	1-(4′-tolyl)-1,3-butanedione (2)	70
3	4′-Chloroacetophenone	5	1-(4′-chlorophenyl)-1,3-butanedione (3)	76
4	4′-Nitroacetophenone	12	1-(4′-nitrophenyl)-1,3-butanedione (4)	75
5	4-Acetylbiphenyl	6	1-biphenyl-1,3-butanedione (5)	78
6	2-Acetylnaphthalene	8	1-(2-naphtyl)-1,3-butanedione (6)	82
7	2-Acetylthiophene	6	1-(2-thenyl)-1,3-butandione (7)	81
8	Cyclohexanone	5	2-acetylcyclohexanone (8)	86
9	4-t-Butylcyclohexanone	6	2-acetyl-4-t-butylcyclohexanone (9)	76
10	2-Cyclohexylcyclohexanone	10	2-acetyl-6-cyclohexylcyclohexanone (10)	72

like species. The intermediate silyl enol ether (I) reacts with acetyl chloride in presence of HCl, which is thought to be a key reaction, to give the intermediate (II) followed by hydrolysis afforded the corresponding acetyl ketones since the medium was acidic. In most cases the process, under our reaction conditions, permit isolation in good yields of the desired products. Yields are nearly quantitative where the diketone-zinc complex as intermediate[10] was not formed as shown in Scheme 2.



SCHEME 2

Extended studies on the acetylation of other function groups such as α, β-unsaturated ketones or nitriles, esters, and amides are currently in progress.

In contrast to the reaction with acid chlorides or acid anhydrides in the presence of basic reagents to produce O-acylate products, the reaction by using TCS/$ZnCl_2$ as a binary reagent represents a novel method of achieving C-acetylation of hindered ketones such as those that exist frequently in the natural products.

The procedure described here appears to offer several advantages over previous methods for the C-acetylation of ketones. It combines generality in acetylation predominant selectivity for C-acetylation over O-acetylation and convenience for the synthesis of C-acetylated products having various types of functional groups.

EXPERIMENTAL

All reactions were carried out under atmospheric conditions at room temperature. Tetrachlorosilane (TCS) was obtained from commercial sources. Anhydrous zinc chloride (prepared by fusion as sod.acetate). The solvent were distilled and dried before use. Reactions were mentioned by TLC on 0.25 mm Merk Silica gel sheets (60 GF 354) (4×2 cm) developed with UV light or I_2 vapor.

The General Procedure

A mixture of the ketone (10 mmol), acetic anhydride (1.89 ml, 20 mmol), tetrachlorosilane (2.4 ml, 20 mmol) in dry dichloromethane (10 ml) was prepared, then anhydrous $ZnCl_2$ (2.72 gm, 20 mmol) was added and the reaction mixture was allowed to stir with exclusion of moisture at ambient temperature (25°C) for a specified time as on Table I. Then it was poured into ice-cold (100 ml) neutralized by Na_2CO_3 solution and extracted with $CHCl_3$ (2×50 ml). The extract was dried over anhydrous Na_2SO_4 and the solvent was removed by distillation, the residue was purified by TLC chromatography using pet.ether (60:80): ethyl acetate (10:1) as eluant for isolate pure products.

1-Phenyl–1,3-butanedione (1)

The general procedure [I] yielded the title compound (1) (1.393 gm, 86%) from acetophenone (1.17 ml, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.62$, m.p. = 58-60°C (Lit.[15] m.p. = 61°C).

IR. (KBr plate). $\nu = 3050$, 3000 (CH, Ar); 2924, 2850 (CH_3, CH_2); 1640–1600 (two/C=O); 1600–1568 (C=C) cm^{-1}.

^{1}H-NMR ($CDCl_3$). $\delta = 16.16$ (s, 1H, enolic); 7.90–7.86 (d, 2H, Ar—H); 7.57–7.42 (m, 3H, Ar—H); 6.19 (s, 1H, olefenic-H); 2.21 (s, 3H, CH_3) ppm.

M.S. (m/z, %): 162 (M^+, 100); 147 (M^+—CH_3, 73.09); 105 (M^+—CH_3-CO—CH_2—, 51); 48 (M^+—Ph, 19.19); 76.95 (C_6H_5, 48.17).

1-(p-Tolyl)-1,3-butanedione (2)

The general procedure [I] yielded the title compound (2) (1.232 gm, 70%) from 4′-Methylacetophenone (1.34 ml, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.61$, m.p. = 56°C (Lit.[15] m.p. = 57°C).

IR (KBr plate): $\nu = 3032$, 2994 (CH, Ar); 2923, 2860 (CH_3, CH_2); 1680–1600 broad (two/C=O); 1600 (C=C) cm^{-1}.

1-(4′-Chlorophenyl)-1,3-butanedione (3)

The general procedure [I] yielded the title compound (3) (1.493 gm, 76%) from 4′-Chloroacetophenone (1.2988 ml, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.52$, m.p. = 70°C, (Lit.[16] m.p. = 72°C).

IR (KBr plate). $\nu = 3090$, 3080 (CH, Ar); 2920, 2850 (CH_3, CH_2); 1640–1610 broad (two/C=O); 1591, 1547 (C=C) cm^{-1}.

1-(4′-Nitrophenyl)-1,3-butanedione (4)

A mixture of ketones (10 mmol), acetic anhydride (3.78 ml, 40 mmol), tetrachlorosilane (6 ml, 50 mmol) in dry dichloromethane as a solvent, then anhydrous $ZnCl_2$(1.36 gm, 10 mmol) yielded the title compound (4) 1.55 gm, 75%) from 4′-nitroacetophenone (1.65 gm, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.46$, m.p. = 111°C (Lit.[15] m.p. = 111–13°C).

IR (KBr plate). $\nu = 3100$, 3090 (CH, Ar); 2923, 2860 (CH_3, CH_2); 1660–1610 broad (two/C=O); 1593 (C=C) cm^{-1}.

1-Biphenyl-1,3-butanedione (5)

The general procedure [I] yielded the title compound (5) (1.84 gm, 78%) from 4-acetylbiphenyl (1.9625 gm, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80):

ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.6$, m.p. = 108–110°C. (Lit.[17] m.p. = 110–112°C).

IR (KBr plate). $\nu = 3093, 3015$ (CH, Ar); 2920–2850 (CH_3,CH_2); 1669, 1650 (two/C=O); 1514 (C=C) cm^{-1}.

1-(2-Naphthyl)-1,3-butanedione (6)

The general procedure [I] yielded the title compound (6) (1.745 gm, 82%) from 2-acetylnaphthalene (1.7 gm, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.58$, m.p. = 80°C (Lit.[18] m.p. = 79–80°C).

IR (KBr plate). $\nu = 3098$, 3015 (CH, Ar); 2920–2850 (CH_3, CH_2); 1680,1640 (two/C=O); 1595 (C=C) cm^{-1}.

1-(2-Thienyl)-1,3-butanedione (7)

The general procedure [I] yielded the title compound (7) (1.360 gm, 81%) from 2-acetylthiophene (1.08 ml, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.46$, m.p. = 38–40°C (Lit.[19] m.p. = 35–37°C).

IR (KBr plate). $\nu = 3090$, 3015 (CH, Ar); 2925–2870 (CH_3, CH_2); 1680–1620 broad (two/C=O); 1570 (C=C) cm^{-1}.

2-Acetylcyclohexanone (8)

The general procedure [I] yielded the title compound (8) (1.18 gm, 86%) from cyclohexanone (1.03 ml, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.32$ (Lit.[20], b.p./mm., 95–5°/10).

IR (KBr neat). $\nu = 2936$, 2862 (CH_3,CH_2); 1708–1640 (two/C=O) cm^{-1}.

2-Acetyl-4-t.butyl Cyclohexanone (9)

The general procedure [I] yielded the title compound (9) by reflux (1.48 gm, 76%) from 4-t.butyl cyclohexanone (1.40 gm, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.0.25$ (Lit.[20], b.p./mm., 120–5°/10).

IR (KBr neat). $\nu = 2959–2870$ (CH_3,CH_2); 1705–1600 broad (two/C=O) cm^1.

2-Acetyl-6-cyclohexyl Cyclohexanone (10)

The general procedure [I] yielded the title compound (10) by reflux (1.60 gm, 72%) from 2-cyclohexyl cyclohexanone (1.857 ml, 10 mmol) and acetic anhydride (20 mmol), which purified by preparative TLC using pet.ether (60:80): ethyl acetate (10:1) as eluent for isolation of pure product, $R_f = 0.28$, m.p. = 46–47.

IR (KBr neat). $\nu = 2950, 2860$ (CH_3, CH_2); 1710, 1650 (two/CO)cm^{-1}.

M.S. (m/z, %): 222 (M^+, 12.34); 207 (M^+—CH_3, 71.39); 179 (M^+—$COCH_3$, 100); 96 (M^+-[Cyclohexyl, $COCH_3$], 46.19); 83 (cyclohexyl, 9.92).

Anal. Calcd. for C14H22O2 (222.32): C, 75.63; H, 9.97. Fopund: C, 75.55; H, 9.92%.

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