The Selective 1,2-Addition of Ketene Silyl Acetals to α,β-unsaturated Ketones Promoted by a Copper(I)-Phosphine Complex

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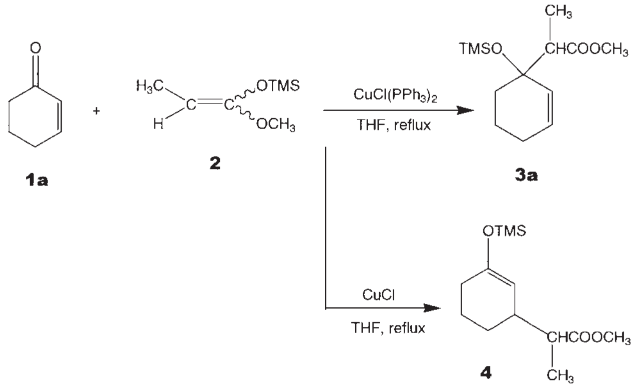
The thermal reaction of an α,β-unsaturated ketones with a ketene silyl acetal in the presence of the copper(I)halide-phosphine complex brought about the selective formation of the products based on 1,2-addition, while use of the copper(I)halide alone afforded the 1,4-adduct type of product.

α,β-unsaturated carbonyl compounds have two alternative modes of addition with nucleophiles, i.e., 1,2- or 1,4-addition. While 1,2-direct addition to a carbonyl group is favored with alkyl lithium reagents[1] which are hard nucleophiles, 1,4-conjugated addition is realized with alkyl copper reagents.[2] Stabilized carbanions also perform direct or conjugated addition depending upon the types of reagent; for example, enolates[3] from β-dicarbonyl compounds or ketones, α-nitro anions,[4] and thioacetal monosulfoxide anions[5] selectively undergo 1,4-addition, α-nitrile anions[6] and dithiane anions[7] effect 1,2- and 1,4-addition. Enolates derived from esters have been reported to prefer 1,4-addition under thermodynamically controlled conditions, while 1,2-addition under kinetically controlled conditions; i.e., although 1,2-adducts are preferentially formed at low temperature ($-78\,^{\circ}$C), warming a reaction mixture to room temperature results in selective formation of 1,4-adducts.[8] Silyl enol ethers and ketene silyl acetals, which have more covalent character than alkali metal enolates, are able to give β-substituted ketones based on 1,4-addition under promotion by a conventional Lewis acid such as titanium tetrachloride.[9] We have previously reported that cuprous chloride catalyzes 1,4-addition accompanying the silyl group transfer of silyl enol ethers and ketene silyl acetals to conjugated enones under photo-irradiation.[10] To contrary to our previous findings, we have recently found that the copper(I)-phosphine complex promotes the 1,2-addition reaction of ketene silyl acetals to conjugated enones under thermal conditions.

At first, a solution composed of 2-cyclohexen-1-one **1a** (2 mmol), the methyl propionate-derived ketene silyl acetal **2** (3 mmol), $CuCl(PPh_3)_2$ (2 mmol) and THF (5 ml) was refluxed for 4 h under a nitrogen atmosphere. VPC analysis of the resulting mixture revealed appearance of one volatile product, which was assigned to be the 1,2-adduct **3a** from spectral data[11] after isolation (52% yield) (Scheme 1). Use of CuCl alone instead of $CuCl(PPh_3)_2$ resulted in selective formation of the 1,4-addition product **4** albeit in a low yield (24%) (Scheme 1). Furthermore, a reaction without CuCl did not form any addition product. Next, a method consisting of in situ preparation of **2** was examined in order to avoid rather troublesome isolation procedure of the ketene silyl acetal. When methyl propionate (3.3 mmol), Me_3SiCl (8 mmol), LDA (3.3 mmol), **1a** (2 mmol), and $CuCl(PPh_3)_2$ (2 mmol) were successively added to a THF solvent (5 ml) in a flask under a nitrogen atmosphere and then refluxed for 4 h, **3a** was obtained in 49% yield, which was almost comparable with that in the procedure using **2** isolated. Again, omitting the copper species from this reaction system did not bring about formation of an addition product. Thus, the investigations were hereafter performed using a method to prepare in situ the ketene silyl acetals. Use of CuBr instead of CuCl gave **3a** in an almost same yield (51%) as that in CuCl.



Scheme 1.

Then, the reactions were performed in some solvents other than THF, in which tributylphosphine was used as a ligand because the triphenylphosphine complex of cuprous bromide was little solved in those solvents except for THF. The results are shown in Table 1. Although the well-defined relationship between yields of **3a** and the polarities of solvents was not observed, it is worth noting that diethyl ether was the best of the examined solvents (Table 1, run 2), while other ether solvents (THF and 1,2-dimethoxyethane) afforded the lower yields of **3a** (Table 1, run 1 and 3) along with remaining of the starting material **1** than the hydrocarbon solvents (i.e., hexane and cyclohexane, Table 1, run 5 and 6). In turn, the reaction using

Table 1. Recation of 2-cyclohexen-1-one **1a** with the ketene silyl acetal generated in situ from methyl propionate

$$\mathbf{1a} + CH_3CH_2COOCH_3 \xrightarrow[\text{solvent, }\triangle\text{, 4h}]{TMSCl/LDA/CuBr/PR_3} \mathbf{3a}$$

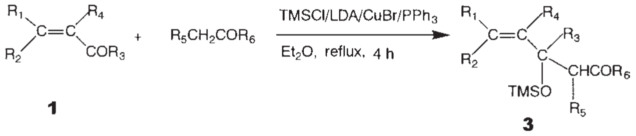
Run	Solvent	Temp./°C	PR_3	**3a** Yield[a]/%
1	THF	66	PBu_3	39
2	diethyl ether	35	PBu_3	63
3	1,2-DME	85	PBu_3	16
4	DMF	70	PBu_3	55
5	hexane	69	PBu_3	57
6	cyclohexane	81	PBu_3	60
7	diethyl ether	35	PPh_3	75 (72)[b]

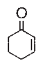
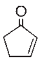
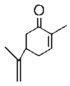
[a]Determined by VPC analysis.
[b]Isolated yield after column chromatography.

triphenylphosphine as a ligand in diethyl ether, although the soluble complex of cuprous bromide was not formed at the initial stage of mixing, was examined, resulting in the better yield than that in the reaction using tributylphosphine (Table 1, run 2 and 7).

Methyl alkanoates other than methyl propionate also gave 1,2-adducts with **1a** in the reaction in a diethyl ether solution containing cuprous bromide and triphenylphosphine.[12] *N*,*N*-dimethylacetamide similarly effected the 1,2-adduct, although in a lower yield (54%) compared with methyl acetate being the corresponding ester analogue. The reactions of methyl propionate with α,β-unsaturated ketones other than **1a** were in turn performed to afford the 1,2-adducts. These results are shown in Table 2, in which the reactions afforded the 1,2-adducts **3** (e.g., run, 5, 7, and 9) in moderate yields with some starting materials remained **1**.

Table 2. Reaction of α,β-unsaturated ketones with ketene silyl acetals generated in situ



Run	1		$R_5CH_2COR_6$	3	Yield[a]/%
1		**a**	$CH_3CH_2COOCH_3$	**a**	75 (72)[b]
2	**a**		CH_3COOCH_3	**b**	86
3	**a**		$CH_3(CH_2)_2COOCH_3$	**c**	93
4	**a**		$CH_3(CH_2)_3COOCH_3$	**d**	73
5	**a**		$(CH_3)_2CHCOOCH_3$	**e**	40
6	**a**		$CH_3OCH_2COOCH_3$	**f**	95
7	**a**		$CH_3CON(CH_3)_2$	**g**	54
8			$CH_3CH_2COOCH_3$	**h**	87 (84)[b]
9			$CH_3CH_2COOCH_3$	**i**	48
10	$CH_2{=}CHCOCH_3$		$CH_3CH_2COOCH_3$	**j**	74
11	$CH_3CH{=}CHCOCH_2CH_3$		$CH_3CH_2COOCH_3$	**k**	86 (82)[b]

[a]Determined by VPC analysis. [b]Isolated yield after column chromatography.

Concerning the reaction mechanism, the activating effect of the Lewis acid such as titanium tetrachloride on the reaction of conjugated enones with silyl enol ethers has been assumed to be brought about by coordination to the oxygen atom of the conjugated enone to enhance its electrophilicity and facilitate attack by silyl enol ethers to form the 1,4-adducts.[13] Actually, use of cuprous chloride alone in our reaction also brought about the 1,4-adduct similarly to promotion by the conventional Lewis acids. Thus, peculiar promotion with the copper(I)-phosphine complex probably operates in our reaction to effect selective formation of the 1,2-adducts, and it might be likely as a working hypothesis that simultaneous coordination of the conjugated enone and the ketene silyl acetal to the copper(I)-phosphine complex triggers the 1,2-addition reaction, although the precise mechanism is unclear at this stage.

Our method necessitates the use of a stoichiometric amount of the copper(I)halide-phosphine complex, which might be owing to its relatively low Lewis acidity as revealed by requisition of rather severe reaction conditions (reflux, 4 h). Thus, possibility that the 1,2-addition reaction of this type may be catalytically performed by using the phosphine complexes of metal species bearing the enhanced Lewis acidities compared with CuBr remains to be investigated. Furthermore, for development of the asymmetric version, the reaction using the chiral phosphine complexes will be a target to be challenged.

References and Notes

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11 Spectral data of **3a**: ^{1}H NMR($CDCl_3/CCl_4$, 60 MHz) δ 0.04 (s, 9H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.52–2.31 (m, 6H), 2.55 (q, $J = 6.8$ Hz, 1H), 3.65 (s, 3H), 5.98 (br.s, 2H); ^{13}C NMR ($CDCl_3/CCl_4$, 15 MHz) δ 1.90, 12.77, 25.06, 31.64, 32.83, 49.14, 50.76, 134.32, 134.86; MS (EI) *m/z* (%) 256 (0.5, M^+), 241 (50), 170 (100), 145 (94), 107 (75), 89 (98), 73 (96); HRMS *m/z* Calcd for $C_{13}H_{24}O_3Si$ 256.1493, Found 256.1521.

12 A typical experiment is as follows. To a solution consisting of an ester (3.3 mmol), TMSCl (8 mmol) and Et_2O (5 ml), LDA (3.3 mmol, 2.0 mol dm^{-3} in heptane/THF/ethylbenzene) was added under nitrogen atmosphere at 0 °C and stirred for 30 min. Then, a conjugated enone (2 mmol), CuBr (2 mmol) and PPh_3 (4 mmol) were successively added and the reaction mixture was refluxed for 4 h. After the solid parts were filtered off, the filtrate was submitted to preparative VPC.

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