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Highly Effective Catalysts for the Conjugate Addition of Silyl Ketene Acetals to Enones (Mukaiyama-Michael Reaction)

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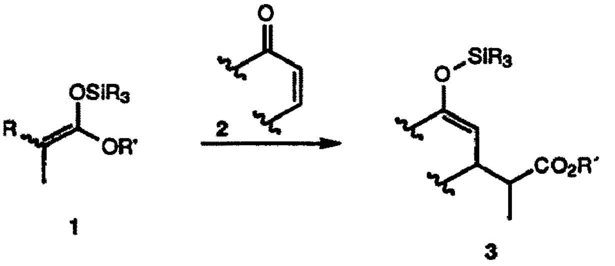
Abstract: Conjugate additions of O-silylated ketene acetals to simple enones have been reported to proceed without a catalyst if acetonitrile is used as solvent. Inability to repeat this procedure led to the discovery that an as yet unknown species formed from P_4O_{10} in acetonitrile displays high catalytic activity.

The Mukaiyama-Michael reaction[1], *i.e.*, conjugate addition of a O-silyl ketene acetal **1** to an α,β-unsaturated carbonyl compound **2**, constitutes a highly efficient method for introducing an acetic acid residue β to a carbonyl group. The utility of the reaction has been demonstrated by numerous applications in natural product synthesis.

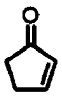
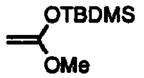
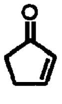
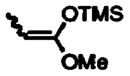
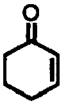
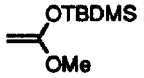
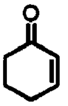
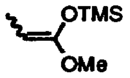
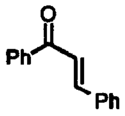
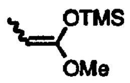


Normally, a catalyst is used to promote the reaction (Lewis acids: $TiCl_4$[1], $LiClO_4$[2]; redox catalysts[3]). However, it was also reported that the reaction can be carried out without a catalyst if acetonitrile is used as the solvent. With simple, sterically undemanding enones, mild heating for a few hours sufficed to give excellent yields[4,5]; but with sterically shielded enones high pressure conditions (6-15 kbar) were required[5].

The present work was initiated because of our inability to repeat the simple, well documented[4a] reactions of silyl ketene acetals[4b] with cyclopentenone. It was reported that heating to 55 °C for 2 hours gave the product in 95 - 98 % yield. However, in our hands at best yields of ca. 10 - 40 % were achieved despite numerous trials, extended reaction times and use of up to 1.3 equivalents of 1 (cf. Table 1, Nos. 1, 7, 11, 15, 18).

It occurred to us that the purity of the solvent acetonitrile may be important: in our laboratory, drying by distillation from CaH_2 is routinely used; but in other laboratories, distillation from P_4O_{10} is employed. As it is known that the latter procedure can give a solvent containing traces of phosphorus compounds, we tried acetonitrile dried with P_4O_{10} : excellent results were indeed obtained (Table 1, Nos. 4, 9, 13). Similarly, when small amounts of P_4O_{10} were added to the reaction mixture in acetonitrile dried with CaH_2, excellent yields resulted (Table 1, Nos. 2, 3, 8, 12, 16, 19).

Table 1: Additions of O-silylated ketene acetals **1** to enones **2**
(solvent: acetonitrile; abbreviations: C = CaH_2, P = P_4O_{10} , P/A = mixture of P_4O_{10} and diisopropylamine; for experimental procedures see Ref. 6).

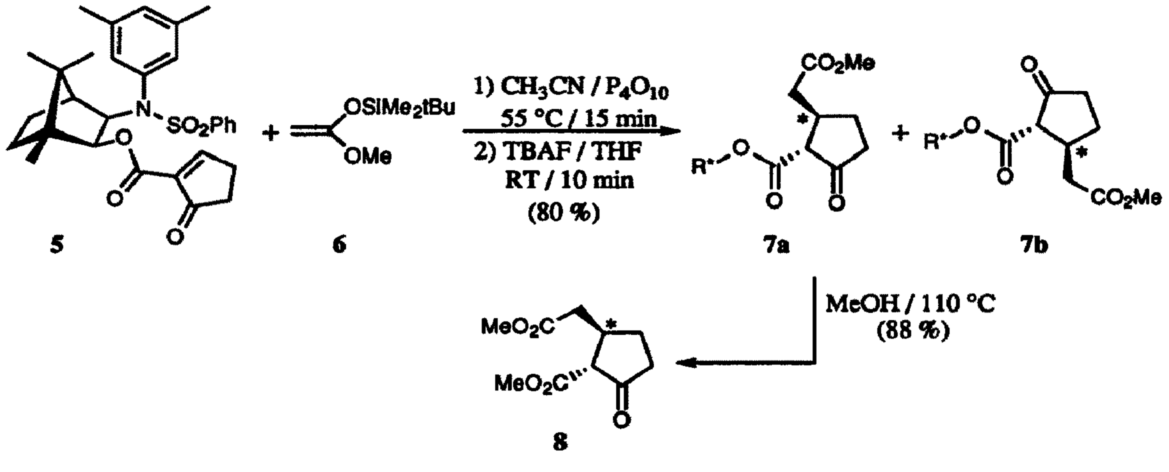
No.	2	1[1]	Drying agent	Catalyst	Temp.	Reac. Time	Yield of 3
					[°C]	[min]	[%]
1			C	-	55	240	5-20
2			C	P	55	4	89
3			C	P	RT	15	90
4			P	-	55	150	88
5			P	P	55	5	91
6			P	P/A	RT	40	92
7			C	-	55	480	14
8			C	P	55	15	90
9			P	-	55	90	89
10			P	P	55	15	92
11			C	-	55	840	29
12			C	P	RT	15	93
13			P	-	55	240	97
14			P	P	RT	60	94
15			C	-	55	480	36
16			C	P	55	10	86
17			P	P	55	10	94
18			C	-	55	480	12
19			C	P	55	15	90
20			P	P	55	15	86

1. O-Silylated ketene acetals were prepared according to the procedure of Kita et al (Ref. 4b).

Optimisation experiments quickly revealed that the reaction when catalysed with P_4O_{10} is extremely fast and gives far better results than under the reported conditions: with stoichiometric amounts of reactants yields of ca. 90 % were obtained in a few minutes at room temperature[6]. The experiments described above led to an even better catalyst. Typically, the distilled reaction products contained, according to NMR spectra, ca. 5-10 % of the corresponding ketones **4**. Initially, we thought this to be caused by the hydrolysis of the moisture sensitive silyl enol ethers **3**. However, the reaction products of the silyl ketene acetals of propionates, prepared according to the procedure of Kita et al.[4b], were found to be pure. NMR spectra of the latter revealed that these contained traces of diisopropylamine. As a consequence, we added this amine to the catalyst solution: the resultant mixture generally gave pure silyl enol ethers. Furthermore, reactions with this catalyst were found to be faster by a factor of ca. 1.7.

Preliminary investigations as to the nature of the catalytically active species were carried out. As dry-box techniques where not employed, we suspected mixtures of phosphorus compounds. Indeed, ^{31}P NMR spectra of mixtures of P_4O_{10} and acetonitrile showed two broad singlets at -31.45 and -45.30 ppm; after addition of diisopropylamine these disappeared and numerous new resonances were observed.

In natural product syntheses, sterically hindered enones have been frequently used[2,5]. Various catalysts or high pressure conditions were found necessary to promote Mukaiyama-Michael additions with these compounds. It so happened that a corresponding substrate, **5**, was at hand in our laboratory[8]. This starting material is an interesting one because it is crystalline and stable, while the corresponding ethyl ester polymerises too rapidly for purification[9].



Under the conditions stated above (CH_3CN / P_4O_{10} cat. / 55 °C) the Mukaiyama-Michael addition of the O-silyl ketene acetal **6** to the enone **5** is very fast (reaction time: 15 min) and gives a mixture of the diastereoisomers **7a** and **7b** in the ratio of 8 : 2, respectively. Stereoselectivity can be improved to 9:1 by employing an equimolar amount of $ZnCl_2{\cdot}OEt_2$ (2.2 M in dichloromethane) in dry acetonitrile. The pure diastereoisomer **7a** (mp 167-168 °C) was obtained in 68 % yield from **5** by crystallisation of the mixture **7a**/**7b** from hexane/ethyl acetate 9:1. The configuration of **7a** was determined after transesterification with methanol to give the dimethylester **8**: $[\alpha]_{589}{}^{20} = -67.1$ (c = 1.42, methanol). This compound was previously prepared by an ex-chiral pool synthesis: $[\alpha]_{589} = -66.8$ (c = 1.42, methanol)[10].

In conclusion, we have found that the reported effectiveness of acetonitrile as solvent for the "non-catalysed" Mukaiyama reaction is most probably due to traces of phosphorus compounds introduced by drying with P_4O_{10}. On the basis of this finding, we have developed a very simple catalyst system that was found to be highly effective with a variety of substrates[11].

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6. Experimental procedures: (a) Under an atmosphere of dry nitrogen, a solution of the enone **1** (1.0 mmol) in dry[7] acetonitrile (1.5 ml) was treated with the silyl ketene acetal **2**. After stirring at 55°C, additional **2** was added portion wise (ca. 0.4 mmol) until TLC monitoring showed no further conversion. The mixture was then filtered through a small column of alumina (activity 2) which was further eluted with Et_2O. The filtrate was concentrated *in vacuo* and the residue purified by Kugelrohr distillation at reduced pressure. (b) As above, except that after mixing of the reactants 0.2 ml of a saturated solution of P_4O_{10} in acetonitrile (concentration: ca. 50 mg/ml; 0.176 M) was added.
7. Acetonitrile was stirred over CaH_2 over-night, then filtered and distilled from CaH_2 or P_4O_{10}.
8. We thank Dr. E. Urban for the procedure to prepare this reagent.
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11. All new compounds gave satisfactory spectroscopic data and elemental analyses.

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