LITHIUM PERCHLORATE CATALYZED CONJUGATE ADDITION OF O-SILYLATED KETENE ACETALS TO HINDERED α,β -UNSATURATED CARBONYL COMPOUNDS AT ATMOSPHERIC PRESSURE

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Abstract: O-Silylated ketene acetals undergo 1,4 conjugate addition to hindered α , β -unsaturated carbonyl systems at atmospheric pressure in the presence of lithium perchlorate.

Several years ago, in connection with our synthetic efforts in the quassinoid area, we attempted to carry out the conjugate addition of the O-silylated ketene acetal derived from methyl acetate to the activated enone 1 (R = Me). Unfortunately efforts to induce this transformation either thermally¹ or under Lewis acid catalysis² employing titanium tetrachloride or a 1:1 mixture of titanium tetrachloride and titanium tetraisopropoxide in methylene chloride gave rise to the Michael adduct 2 (R = Me) in < 10% yield.³ In those instances where the thermal Michael reaction is sluggish due to sterically hindered substrates or in cases where Lewis acid promoted reactions are not compatible with existing functionality, ultrahigh pressure has been employed to accelerate conjugate addition reactions.^{3,4} We wish to report that silyl ketene acetals add in a conjugate fashion to highly functionalized, hindered α , β -unsaturated carbonyl systems in the presence of lithium perchlorate at atmospheric pressure (cf Equation 1), thus obviating the necessity of utilizing ultrahigh pressure.



In a preliminary experiment, a 0.2 M solution of activated enone 1 (R = Me) in 1.0 M LiClO₄-Et₂O at ambient temperature was exposed to 6.0 equiv of 1-methoxy-1-(t-butyldimethylsiloxy)ethylene. After 1 h a 70% yield of 2 (R = Me) and the corresponding 1,2-addition product were obtained in a ratio of 1.8:1. Increasing the concentration of lithium perchlorate in diethyl ether further enhanced the ratio of the 1,2addition product over the 1,4-adduct. Exclusive formation of the 1,4-addition product could be realized by employing 1.0 M LiClO₄ in dimethoxyethane, however, the reaction rate is appreciably slowed in DME. Treatment of a 0.1 M solution of tricyclic activated enone 1 (R = Me) in 1.0 M LiClO₄-DME with 10.0 equiv of 1-methoxy-1-(t-butyldimethylsiloxy)ethylene at 36° for 24 h gave rise to a 93% yield of the 1,4-addition product 2 (R = Me). Similar results were obtained with substrate 1 (R = TBDMS). Exposure (37°C) of 1 (R = TBDMS) [0.1 M in 1.0 M LiClO₄-DME] to excess silyl ketene acetal for 13 h afforded a near quantitative yield of product 2 (R = OTBDMS). In both cases only a single adduct is produced in the Michael reaction and in each case the product possesses the C(14) α -stereochemistry.

The lithium perchlorate catalyzed Michael reaction has been carried out on a number of substrates (see Table 1) including sterically demanding β , β -disubstituted unsaturated carbonyl systems. In general, reactions are conducted at ambient temperature and pressure. The solvent of choice for the majority of systems examined is 1.0 M LiClO₄ in diethyl ether, however more demanding situations require increasing the concentration of lithium perchlorate (<u>vide infra</u>). Silyl ketene acetals **3** and **4** also undergo 1,4-addition. For example, exposure of cyclohexenone (0.1 M in 1.0 M LiClO₄-Et₂O) to 5.0 equiv of **3** for 30 min gave rise to an 87%



yield of 5. The more demanding silyl ketene acetal 4 required the use of 5.0 M LiClO₄-Et₂O. Treatment of a 0.1 M solution of cyclohexenone in 5.0 M LiClO₄-Et₂O with 5.0 equiv of 4 afforded after 1.6 h a 76% yield of 6. No reaction was observed with 1.0 M LiClO₄-Et₂O.

Lithium perchlorate has also been used to catalyze the conjugate addition of silyl ketene acetals to α , β -unsaturated δ -lactones. Treatment of a 0.1 M solution of the functionalized δ -lactone 7



in 2.5 M LiClO₄ in diethyl ether at ambient temperature with 5.0 equiv of 1-methoxy-1-(t-butyldimethylsiloxy)ethylene gave rise within 15 min to an 85% yield of lactone 8. In similar fashion, a 0.1 M solution of unsaturated lactone 9 in 2.5 M LiClO₄-Et₂O was transformed (R.T., 2 h, 65%) into 10, a key intermediate in a recently completed total synthesis of the cytotoxic natural product sesbanimide A.⁵







The conjugate additions to lactones 7 and 9 above do proceed in 1.0 M LiClO₄-Et₂O, however, the reactions are appreciably slower and give rise to slightly decreased yields.

The mildness and efficiency of the lithium perchlorate catalyzed conjugate additions of O-silylated ketene acetals to α , β -unsaturated carbonyl systems will find considerable use in organic chemistry.

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