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Highly Efficient and Selective Displacement of Alkylthio group on Acylketene O,S-acetals by Organocopper Reagents: A Novel Route to 2-Alkoxy/aryloxy-1-alkenylketones

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Abstract : Acylketene O,S-acetals **1a-k** undergo efficient and selective conjugate displacement of alkylthio group with organocopper(I) reagents to afford the corresponding β-alkoxy/aryloxy enones **2-21** in good yields.

Carbon-carbon bond forming process *via* conjugate addition of organocuprate reagents to α,β-unsaturated carbonyl compounds represents one of the most versatile synthetic procedures in organic chemistry.[1] Among several variations of this reaction, the conjugate addition - displacement of these reagents to α,β-unsaturated carbonyl compounds containing a good leaving group at the β-carbon (ie. halide,[2] acetate,[3] phosphate,[4] alkoxy[5,6e] and alkylthio[6] substituents) has been actively investigated in the recent years. Substitution of the leaving group by the alkyl ligand of the organocopper reagents generally affords β-alkyl α,β-unsaturated carbonyl compounds stereoselectively although bisconjugate addition becomes competetive with more reactive cuprates and substrates to give β,β-dialkyl carbonyl compounds. Only a few studies however, have been reported with the substrates containing two leaving groups at the β-carbon of the α,β-unsaturated carbonyl compounds. The α-oxoketene dithioacetals having two β-alkylthio groups are the sole substrates studied under this category.[7] Replacement of the single methylthio group in these compounds by the alkyl ligand of the cuprates afford vinylogous thiolesters in highly chemo- and stereoselective fashion.[7] The acylketene O,S-acetals **1** carrying two different heteroatom leaving groups (alkoxy and alkylthio) at the β-carbon appear to be attractive substrates for studying chemoselective displacement of either of these functionalities by organocopper reagents. We herein report our results of this investigation which show highly efficient and selective displacement of only alkylthio group in **1** by a variety of organocopper reagents to afford β-alkoxy/aryloxy-1-alkenylketones exclusively in high yields. This, to our knowledge is the first general study of the reaction of organocopper reagents to α,β-unsaturated carbonyl compounds with two different leaving groups at β-carbon.[8]

The reaction of **1a**[9] with various organocopper reagents (Bu$_2$CuLi, Bu$_2$CuLi.SMe$_2$, Bu(PhS)CuLi, BuMgBr/catalytic CuCN or CuCl) were investigated.[7] Most of the reactions with these reagents were only partially chemoselective and involved addition of either two or three alkyl groups to afford β-alkylated or β-tertiary alkylketones. However, high degree of chemoselectivity was observed when **1a** was reacted with BuCu(Cl)MgBr (2 eqv.), to afford β-methoxyenone **2** exclusively in 82% yield.[10,11] Apparently the substitution of methylthio group in **1a** by the organocopper reagent is more facile than the methoxy group. The reaction was found to be equally facile with other alkylcopper compounds derived from various Grignard reagents (Table, entries 2-6). Similarly, the O,S-acetals having higher alkoxy side chain (entry 7) and the corresponding O-benzylacetal (entry 8) also underwent facile chemoselective substitution of thiomethyl group to afford the corresponding β-alkoxyenones **8** and **9** in 81 and 73% yield respectively. Entries 9-11 represent addition of arylcopper reagents to these substrates to afford the respective β-aryl-β-alkoxyenones in high yields. It is noteworthy (entries 9,10) that both the isomeric β-methoxyenone **10** and **11** could be synthesized in highly regiospecific fashion by this route. The corresponding 2-thienyl (entry 12) O,S-acetal **1e** also underwent conjugate addition - elimination with organocopper reagents to afford the respective product **13** in good yield. The β-methoxyenones **14** and **15** derived from aliphatic 1,3-diketones could also be synthesized in moderate yields by reacting acylketene O,S-acetal **1f** with ethyl and butylmagnesium iodide derived alkylcopper reagents (entries 13 and 14). The methodology could be further extended for the synthesis of hitherto unreported β-aryloxy α,β-unsaturated ketones **16-18** by chemoselective displacement on the corresponding O-aryl-S-alkylketene dithioacetals **1g-h** (entries 15-17). Finally the O,S-acetals **1i-k** from cyclic ketones also underwent facile displacement with these reagents to afford the corresponding enones **19-21** exclusively in good yields (Scheme 2).

In conclusion, we have demonstrated that acylketene O,S-acetals having different β-heteroatom leaving groups undergo highly chemoselective conjugate addition and elimination of methylthio group with organocopper reagents to afford wide range of regiospecifically substituted unsymmetrical β-alkoxy/aryloxy enones. The chemistry of these class of compounds has not been much studied because of their limited availability[12] due to the lack of general procedure for their synthesis. The usual methods for the preparation of these compounds involve (a) reaction of 1,3-diketones with diazomethane[13a-c] or alkyl orthoformate[13d,e] (b) base catalysed O-alkylation of 1,3-diketones[14] (c) nucleophilic displacement of alkoxide ion on β-chloro,[15] β-sulphinyl[16] α,β-unsaturated carbonyl compounds.[15] The first two methods suffer from lack of regioselectivity yielding isomeric mixtures of β-alkoxyenones, whereas the last method requires not easily accessible precursors. The present procedure from acylketene O,S-acetals with built-in alkoxy and aryloxy groups provide a novel and practical route to these compounds in highly chemo- and regioselective manner. Further, the reaction is also applicable for the synthesis of hitherto unknown β-aryloxyenones. However, the general applicability of this methodology depends on the ready availability of acylketene O,S-acetals from aliphatic, acyclic and cyclic ketones. Our efforts to explore further versatality and limitations of this new method as well as synthetic applications of these newly synthesized alkoxy/aryloxyenones are in progress, which will be reported in due course.

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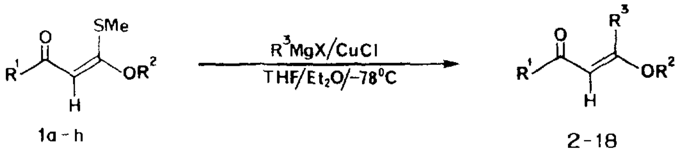
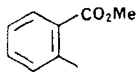
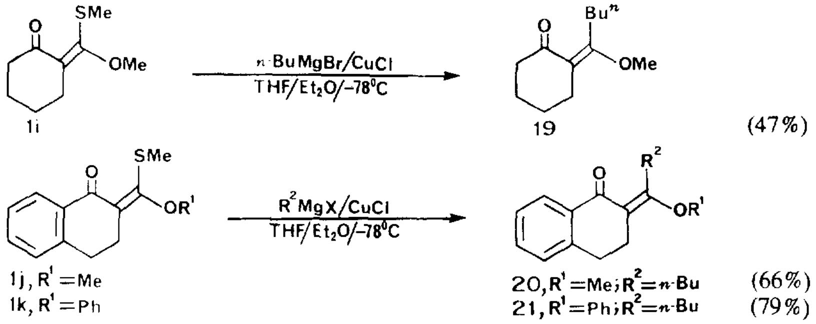


Scheme 1

Table : Synthesis of 2-Alkoxy/aryloxy-3-alkenyl ketones from Acyl ketene O,S-acetals

Entry	1	R^1	R^2	R^3	2-18	% yield
1	**1a**	Ph	Me	Bu	**2**	82
2	**1a**	Ph	Me	Me	**3**	71
3	**1a**	Ph	Me	C_7H_{15}	**4**	77
4	**1b**	4-$MeOC_6H_4$	Me	^{i}Pr	**5**	84
5	**1b**	4-$MeOC_6H_4$	Me	$C_{12}H_{25}$	**6**	78
6	**1b**	4-$MeOC_6H_4$	Me	Allyl	**7**	47
7	**1c**	Ph	^{n}Pr	Bu	**8**	81
8	**1d**	Ph	$C_6H_5CH_2$	Et	**9**	73
9	**1a**	Ph	Me	4-$MeOC_6H_4$	**10**	73
10	**1b**	4-$MeOC_6H_4$	Me	Ph	**11**	68
11	**1d**	Ph	$C_6H_5CH_2$	Ph	**12**	79
12	**1e**	2-Thienyl	Me	Bu	**13**	86
13	**1f**	Me	Me	Et	**14**	63
14	**1f**	Me	Me	Bu	**15**	57
15	**1g**	Ph	Ph	Me	**16**	68
16	**1g**	Ph	Ph	Bu	**17**	79
17	**1h**	Ph		Bu	**18**	86



Scheme 2

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10. Typical procedure for conversion of **1a** into **2**: To a stirred suspension of CuCl (1.0g, 0.01 mol) in 25 ml of dry THF under nitrogen atmosphere at -78°C, BuMgBr [0.01 mol, prepared from magnesium (0.5g, 0.02 mol) and n-butyl bromide (1 ml, 0.01 mol) in 60 ml of Et_2O : THF (1:3)] was added dropwise and the reaction mixture was further stirred for 20 min followed by addition of **1a** (1 g, 0.005 mol) in THF (15 ml) at -78°C. The reaction mixture was continuously stirred for 45 min (monitored by tlc) at the same temperature, poured into satd. NH_4Cl solution (100 ml), extracted with $CHCl_3$ (3x50 ml), dried (Na_2SO_4) and evaporated to give crude **2** which was purified by column chromatography over silica gel using hexane-EtOAc (99:1) as eluents; Viscous liquid (82%); IR ν_{max} (CCl_4) 1746, 1635, 1507, 1196 cm^{-1}; ^1H NMR ($CDCl_3$; 300 MHz) δ 0.94 (3H, t, CH_3), 1.34-1.47 (2H, m, CH_2), 1.55-1.65 (2H, m, CH_2), 2.84 (2H, t, CH_2), 3.75 (3H, s, OCH_3), 6.10 (1H, s, $=CH$), 7.40-7.50 (3H, m, Ar*H*), 7.88-7.92 (2H, m, Ar*H*); m/z 218 (M^+, 10%), 219 (33), 105 (100).
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