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A new method for formacetal linkage formation: protection of alcohols, phenols and carboxylic acids

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Abstract—A new formacetal linkage ($ROCH_2OR'$) forming reaction was developed, which exploited a combination of sulfide ($R'OCH_2SR''$) and $CuBr_2$-Bu_4NBr. This reaction proceeded to give high yields under neutral conditions and was applied to the protection of alcohols, phenols and carboxylic acids by several types of α-oxymethyl groups.

For construction of the complex architecture of biologically significant molecules (e.g. natural products, oligopeptides, oligonucleotides, oligosaccharides, etc.), efficient manipulation of various functional groups is essential, which has to be performed in a chemoselective manner. To that end, the proper choice of protecting groups is critical.

α-Oxymethyl (formacetal) groups ($ROCH_2O$-) have several attractive features as oxygen protection groups.[1] While they can be introduced in a uniform manner using chloride ($ROCH_2Cl$), the stability and conditions required for deprotection are solely dependent upon the nature of the R–O linkage. As a result, one can use multiple types of formacetal groups in an orthogonal sense. Under certain circumstances, formacetal is advantageous over the corresponding ether-based protection (RO-) because the local steric hindrance imposed by the former tends to be much smaller, particularly in the case of bulky R groups (e.g. trialkylsilyl, *t*-butyl, trityl).

The scope of formacetal type protection is currently limited by the availability of requisite α-oxymethyl chlorides, which should be stable enough for isolation. They are usually prepared from the corresponding sulfide ($ROCH_2SMe$) and sulfuryl chloride.[2] Most probably, the compatibility of these conditions with sensitive R groups is limited. On the other hand, the substrate itself should be tolerant to the base that is required for incorporation on formacetal.

We report here a novel protocol for formacetal linkage formation, which would remove the limitations inherent in the conventional method. Our method makes use of a combination of sulfide ($ROCH_2SMe$) and $CuBr_2$-Bu_4NBr.[3,4] The former species is easily obtainable as a stable entity, in most cases from alcohol (ROH) and chloromethyl methyl sulfide ($ClCH_2SMe$), and the latter binary system is essentially neutral, inexpensive, and easy to handle.

As exemplified for the reaction of galactose derivative **1** with **2a**[5] (Scheme 1), protection with the (4-methoxybenzyloxy)methyl (MPMOM) group proceeded smoothly to afford **3a** in high yield. With various functionalized sulfides (**2a**, **2b**,[6] **2c**, **2d**,[7] **2e**[8]), the installation of a range of formacetal groups having valuable features [i.e. oxidant removable (**3a**), fluoride anion removable (**3b**,**e**[8]), fluorophoric (**3c**), and acid-sensitive (**3d**)] was successful. Reactions with fructose derivative **4** as well as tertiary (**5** and **6**) and phenolic (**7** and **8**) OH groups proceeded in a highly satisfactory manner. Dichloromethane and DMF afforded similar results (Table 1).

Under similar conditions, the protection of carboxylic acids was examined using **9**–**14**. It was fully compatible with the presence of ester, amide, and carbamate groups (Table 2). A typical example is shown for the protection of serine derivative **11** (Scheme 2). A series of α-oxymethyl esters obtainable here should have valuable features. For instance, an MPMOM ester can be cleaved by DDQ, toward which the 4-methoxybenzyl ester is known to be resistant. The silyloxymethyl ester (e.g. **15**) is much more stable than the corresponding

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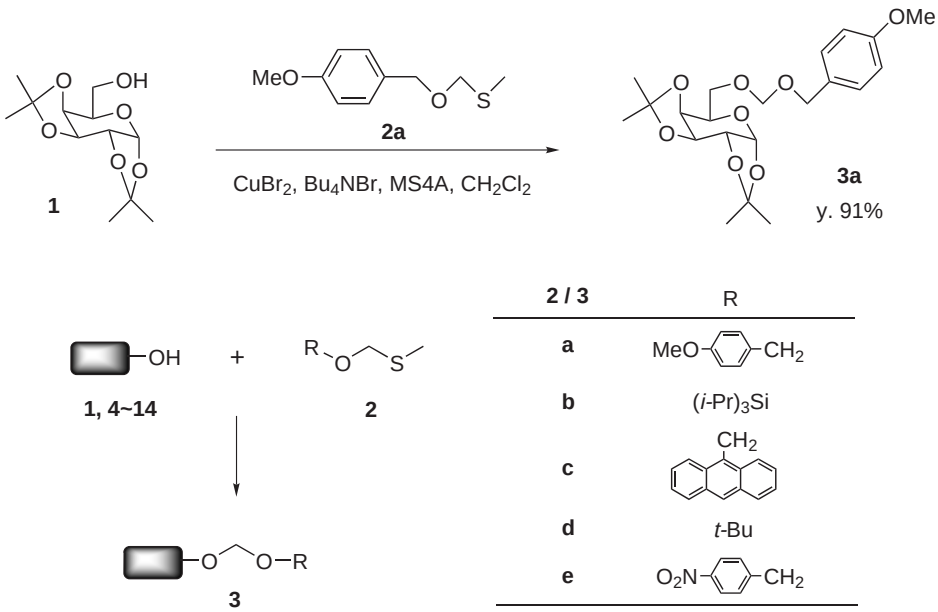
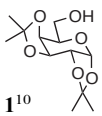
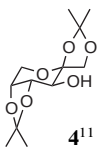
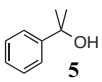
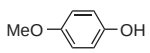
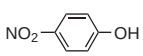


Scheme 1.

Table 1. Protection of hydroxyls and phenols

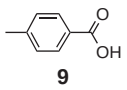
R^1OH	**2** (equiv.)	Solvent	Temp. (°C)/time (h)	Yield (%)
 **1**[10]	**a** (1.2)	CH_2Cl_2	rt/1	91
	a (1.2)	DMF	rt/1	92
	b† (1.9)	CH_2Cl_2	rt/3	92
	c (1.2)	CH_2Cl_2	0/5	92
	d (1.5)	CH_2Cl_2	rt/4	69
	d (3)	CH_2Cl_2	0/4	91
	e (3)	CH_2Cl_2	rt/4.5	77
 **4**[11]	**a** (1.5)	$DMF+ClCH_2CH_2Cl$	rt/2	84
	c (1.2)	$DMF+ClCH_2CH_2Cl$	rt/7	94
	d (5)	CH_2Cl_2	0/4	92
 **5**	**a** (1.5)	CH_2Cl_2	0/27	58
	a (3)	CH_2Cl_2	0/4	80
	b† (3)	CH_2Cl_2	rt/4.5	90
	e (5)	CH_2Cl_2	rt/2.5	70
 **6**	**a** (1.2)	CH_2Cl_2	rt/5	63
	a (3)	CH_2Cl_2	0/3	68
	b† (3)	CH_2Cl_2	rt/28	78
 **7**	**a** (1.2)	CH_2Cl_2	0/5	95
	b† (1.5)	CH_2Cl_2	rt/18	100
 **8**	**b**† (1.5)	CH_2Cl_2	rt/17	85

† $(i\text{-Pr})_3SiOCH_2SEt$.

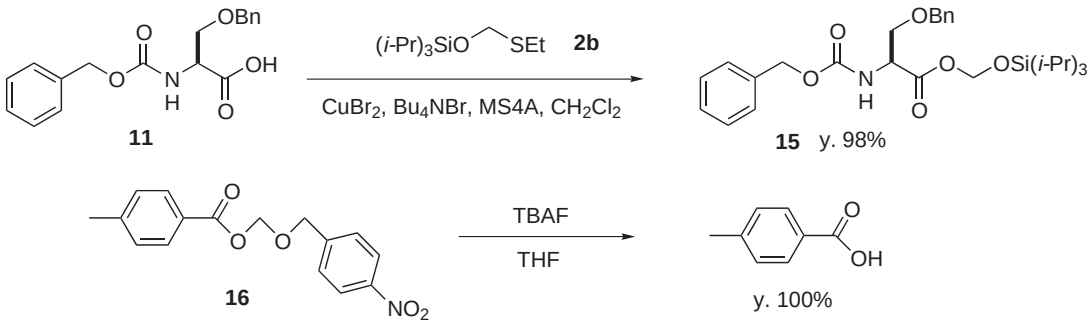
silyl ester, while retaining the Bu_4NF cleavable nature.[9] The 4-nitrobenzyloxymethyl ester would be an additional alternative, since it also has the fluoride sensitivity as demonstrated for **16**[8] (Scheme 2).

In summary, we have developed a novel and flexible method for the formation of a formacetal linkage. It was shown to be effective for the protection of alcohols, phenols, and carboxylic acids. This method utilizes

Table 2. Protection of carboxylic acids

R^1OH	**2** (equiv.)	Solvent	Temp. (°C) / time (h)	Yield (%)
 **9**	**a** (1.5) **b**† (1.5) **e** (1.5)	CH_2Cl_2 CH_2Cl_2 CH_2Cl_2	rt / 4 0 / 4 rt / 24	88 92 63
Boc-Gly-OH (**10**)	**a** (1.5) **b**† (1.5)	DMF CH_2Cl_2	0 / 24 0 / 22	78 93
Z-Ser(Bzl)-OH (**11**)	**a** (3) **b**† (3)	CH_2Cl_2 CH_2Cl_2	0 / 27 rt / 4	100 98
Z-Asp-α-OBzl (**12**)	**a** (3)	DMF	0 / 28	100
Fmoc-Gln(Trt)-OH (**13**)	**b**† (3)	CH_2Cl_2	0 / 16	95
Fmoc-Leu-Ser (ΨMe, Me)pro-OH (**14**)	**b**† (3)	CH_2Cl_2	0 / 28	89

† $(i\text{-Pr})_3SiOCH_2SEt$.



Scheme 2.

readily available sulfide $ROCH_2$-SMe (or -SEt) and can be performed under neutral and mild conditions.

Typical experimental procedure

To a mixture of triisopropylsilyloxymethy ethyl sulfide (**2b**) (78 mg, 0.315 mmol), *Z*-Ser(Bzl)-OH (**11**) (34 mg, 0.105 mmol), and molecular sieves 4 Å (0.2 g, preactivated at 180°C under vacuum) in CH_2Cl_2 (2 mL), were added Bu_4NBr (102 mg, 0.315 mmol) and $CuBr_2$ (70 mg, 0.315 mmol) successively at 0°C. After stirring for 4 h at room temperature, the mixture was filtered through Celite and was then washed with ethyl acetate. The filtrate was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was back-extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue that was purified by silica gel chromatography (ethyl acetate/hexane 1:10→1:6) to give ester **15** (52 mg, 98%) as a colorless oil.

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