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Graphical Abstract

Copper(II) bromide as efficient catalyst for acetal to bisarylmethyl ether interconversion.

R. Mezaache, H. Harkat, J. Obszynski, A. Benkouider, A. Blanc, J.-M. Weibel,* P. Pale*

Dep[t] de pharmacie, Faculté de médecine, Université de Batna, Batna, Algeria, and Laboratoire de synthèse, réactivité organiques et de catalyse, Institut de Chimie, UMR7177-CNRS, Université de Strasbourg, 67070 Strasbourg, France.

Acetals are conveniently and regioselectively transformed into monoprotected diols in the presence of bis(methoxyphenyl)methyl cation source and copper bromide in acetonitrile. The new reagent BMPMOiPr proved to be the most efficient for transprotection with 1,3-dioxolanes and 1,3-dioxanes.

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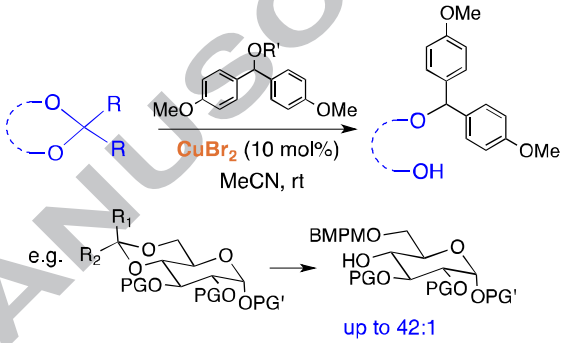

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TETRAHEDRON LETTERS

Copper(II) bromide as efficient catalyst for acetal to bisarylmethyl ether interconversion.

Rofia Mezaache,[a,b] Hassina Harkat,[a,b] J. Obszynski,[b] Abdelhamid Benkouider,[a] Aurélien Blanc,[b] Jean-Marc Weibel[b*] and Patrick Pale[b*]

[a] *Département de Pharmacie, Faculté de Médecine, Université de Batna, Batna 05000, Algeria*

[b] *Laboratoire de synthèse, réactivité organiques, et de catalyse, Institut de Chimie, UMR7177-CNRS, Université de Strasbourg, 4 Rue Blaise Pascal, 67070 Strasbourg, France*

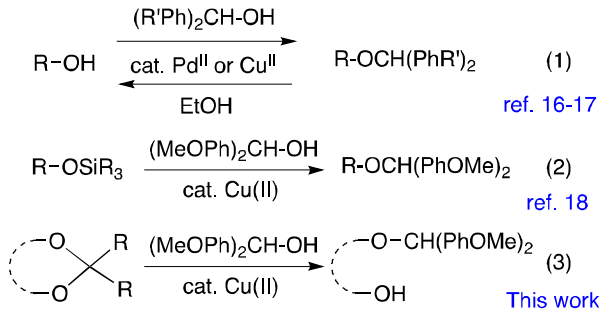
Abstract: — Transprotection of acetals to bis(methoxyphenyl)methyl (BMPM) ethers can be efficiently achieved in the presence of copper dibromide as catalyst in acetonitrile at room temperature. Acetals are conveniently and selectively converted to the corresponding mono-protected diol with bis(methoxyphenyl)methyl isopropyl ether (BMPMOiPr) as reagent. This new practical reagent allows the BMPM transfert to 1,3-dioxolanes or 1,3-dioxanes under copper catalysis. The reaction conditions are also very mild and tolerant to various functional groups, including other protecting groups.

Keywords— protecting group; transprotection, acetal, alcohol; copper, bis(methoxyphenyl)methyl;

Acetal is the most common functional group in Nature, due to its ubiquitous presence as glycosidic linkage in carbohydrates and most glycoconjugates, the most abundant natural products on Earth.[1] Other natural products, such as ionophore antibiotics[2] and some pheromones,[3] also contain such motif, mostly as spiroketal. Acetals are also common protecting groups in organic synthesis.[4]

Despite their interest, acetal protecting groups sometimes require to be exchanged by another group, especially in total synthesis due to compatibility reasons,[5] and more recently, for the valorization of glycerol from biomass as gasoline or diesel additives.[6] Classically achieved through deprotection and reprotection, such sequence would be more convenient by direct exchange. Although valuable, such transprotections, converting one protecting group to another, usually from a different orthogonal set, are surprisingly scarce.[4a]

Known transprotections include the transformation of enol ethers into ketals[7] or thioketals,[8] the conversions of silyl or THP ethers into benzyl ethers or esters,[9] including acetates,[10] alkyl ethers to esters,[10a, 11] thioesters into thioethers or thioketals,[12] allyl carbamates into amides,[13] *N*-Fmoc into *S*-fluorenylmethyl in cysteine and peptides.[14]



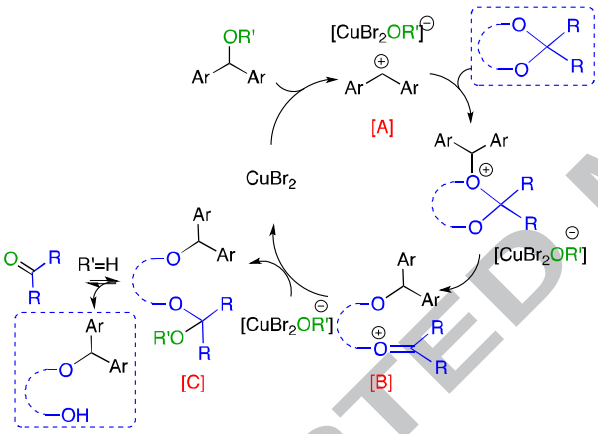
Scheme 1. Diarylmethyl derivatives as protecting group: Palladium and copper-promoted protection or deprotection of alcohols (eq.1); copper-promoted transprotection of silyl ethers (eq. 2) and the present transprotection of acetal (eq. 3).

Following our work on diarylmethyl ethers[15] as alcohol protecting groups revealing their orthogonal protection and deprotection compared to classical benzyl-type groups using palladium(II) salts[16] or copper(II) bromide[17] as catalysts (Scheme 1, equation 1), we recently showed that copper(II) bromide can catalyze the interconversion of silyl ethers to bis(methoxyphenyl)methyl (BMPM) ethers (Scheme 1, equation 2).[18] We now report the transprotection of acetonides and related acetals to our

* Corresponding author. Tel.: +33 368 85 15 xx; fax: +33 368 85 xx xx; e-mail: jmweibel@unistra.fr.
* Corresponding author. Tel.: +33 368 85 15 17; e-mail: ppale@unistra.fr.

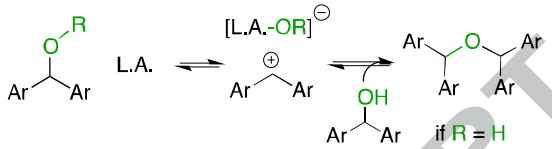
recently introduced bis(methoxyphenyl)methyl (BMPM) ethers (Scheme 1, equation 3).

The results gained from our preceding investigations with silyl ethers[18] suggested a mechanism involving the transient formation of an ion pair with a hydroxycuprate and a bisbenzhydryl-type carbocation (**A** in Scheme 2), the latter acting as Lewis acid toward the oxygen atom of a silyl ether ultimately leading to transprotection. If true, this suggests to use this ion pair toward acetals (Scheme 2). Indeed, interaction and ligation of the bisbenzhydryl-type carbocation to one acetal oxygen would give the oxonium species **B**, in which the acetal would be broken and one oxygen would be already converted to ether. Hydroxide ion transfer from the hydroxycuprate anion would then generate the corresponding ether hemiacetal **C**, giving the transprotected product, while regenerating the copper catalyst. Furthermore, the size of the bisbenzhydryl moiety could lead to regioselective opening of the acetal, as in the well known reductive opening of acetals, especially in carbohydrate chemistry,[19] and impede the further protection of the so-formed hydroxy group.



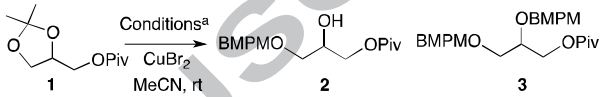
Scheme 2. Proposed mechanism for the Cu(II)-catalyzed interconversion of acetals into BMPM ethers.

To explore this chemistry, we submitted acetonides derived from glycerol to the best conditions achieved for the transprotection from silyl to diarylmethyl ethers, *i.e.* with copper(II) bromide (10 mol%) in acetonitrile at room temperature.[18] As shown in our earlier work in this area, bis(methoxyphenyl)methanol (BMPM-OH) partly dimerized in this reaction, but the so-formed ether $(BMPM)_2O$ disappeared during the reaction course, probably being in equilibrium with the ion pair already mentioned (Scheme 3; R=H). The latter can be a source of the bisbenzhydryl-type carbocation and thus used as reagent. On the other hand, this equilibrium could be controled and even suppressed depending on the leaving group ability of the OR moiety (Scheme 3) if diarylmethyl ethers or esters are used as reagent. Therefore, we first examined the importance of the BMPM sources. The acetonide of glycerol monoprotected with a pivaloyl group **1** was submitted to various BMPM derivatives in the presence of copper dibromide (Table 1).



Scheme 3. Lewis acid-promoted dissociation of diaryl ethers.

Table 1. Screening of conditions for the acetal to BMPM ether interconversion.[a]



Entry	Reagent	Time (h)	Conv. (%)[b]	Yield (%)[c] **2:3**
1	BMPMOH	8	85	72
				3:1
2	$(BMPM)_2O$[d]	4.5	100	100
				1:1
3	BMPMOAc	48	50	32
				1:0
4	BMPMOMe	6.5	50	46
				4:1
5	BMPMO*i*Pr	4.5	100	88
				3:1
6	BMPMO*i*Pr without $CuBr_2$	4	0	-[e]

a) [BMPM-OR]= 1.1 M, [Acetal]= 1 M, [Cu^{2+}]= 0.1 M; b) based on the recovered starting materials; c) cumulative isolated yield of **2** and **3**, without taking into account conversion; d) 0.55 equiv was used; e) starting material recovered.

As expected, BMPM-OH gave transprotection products in high yield, although the conversion was not complete even after 8 h (entry 1). As anticipated (see above), the monoether **2** was selectively produced. The multiplicity of the hydrogen atom of the hydroxyl group in ^{1}H NMR in deutered benzene (doublet at 2.35 ppm) allowed to unambiguously determine the structure of compound **2**. However, and quite surprisingly, **2** was also accompanied by the corresponding diether **3** in which the acetal was fully replaced by two ethers. The latter was caracterized by the presence in ^{1}H NMR spectra of two methine hydrogens from both benzhydryl moiety (5.71 and 5.25 ppm in C_6D_6). The *in situ* formation of $(BMPM)_2O$ (see scheme 3) also led to the concomitant formation of water, leading to 10% of 2,3-dihydroxypropyl pivalate through a more conventional mechanism (entry 1).[20] Starting from the

dimer mentioned above $(BMPM)_2O$, both compounds **2** and **3** were equally produced. Interestingly from a mechanism point of view (see below), the reaction was rather fast and very efficient, with an almost quantitative transprotection (entry 2). On the other hand, the BMPM acetate led to the sole formation of the monoether **2** but with half conversion despite a very long reaction time (entry 3). Surprisingly, simple BMPM ethers proved effective and selective, but to various extends depending on their ether moiety. With the methoxy BMPM, only half conversion could be achieved after 6.5h, but a good selectivity in favor of **2** was observed (entry 4). In sharp contrast, the *iso*propoxy BMPM rapidly and almost quantitatively provided the monoether **2** as the main product, still with the diether **3** but with a good selectivity in favor of the former (entry 5). Control experiment without copper salt did not lead to any transformation and only the starting materials were recovered (entry 6).

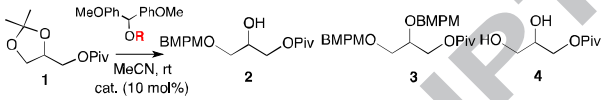
Copper bromide (II) proved to be the most efficient catalyst for the protection and deprotection of alcohol as diarylmethylethers, as well as for the interconversion of silyl to diarylmethyl ethers.[17-18] To be sure that this catalyst was also the best for the present acetal-to-BMPM ether interconversion, we screened several other metal salts as catalysts with the two best BMPM reagents identified above (Table 2). Except palladium salts, the examined Sc, Fe, Au, In catalysts also led to the mono- and diether **2** and **3** (entries 1-11 and 13 vs entry 12). Oxophilic catalysts such as iron, scandium or indium salts did not lead to full conversion, except copper salts (entries 1-5 and 7-12 vs entries 6 and 13).[21] The less oxophilic gold salts gave variable results, but less effective than those achieved with copper salts. Copper(II) bromide proved to be again the best catalyst for the transprotection of acetal to BMPM ethers.

Solvents were also briefly screened. Performing the reaction in the less coordinating THF did not change much the outcome but led to longer reaction time (entry 14 vs 13). Surprisingly, in dioxane, the reaction turned out to be very slow, and even after a day, the starting acetal **1** was still the major compound together with the monoether **2** (entry 15 vs 13). In a non-coordinating solvent such as dichloroethane, the reaction still proceeded but as expected, slowly although less than in dioxane (entry 16 vs 15). Despite a modest conversion, the monoether **2** was strongly favored under these conditions.

The product of deacetalization, diol **4**, could also be detected in small amounts (≤ 12%) in most cases, except with copper salts in acetonitrile (Table 2, entries 1-5 vs 6). These observations tend to support a direct transprotection for the copper-catalyzed version.

With these results in hand, we then briefly examined the scope and limitation(s) of this copper-catalyzed transprotection (Table 3). Various acetals were thus prepared and submitted to the best conditions we found, *i.e.* with BMPM-O*i*Pr as reagent and with 10 mol% of copper dibromide in acetonitrile at room temperature. It is worth noticing that different functional groups have been introduced in the selected acetals in order to look at their compatibility with the reaction conditions.

Table 2. Screening of catalysts for the acetal-to-BMPM ether interconversion.[a]



Entry	R	Cat.	Time (h)	Yield 1(%)[b]	Yield 2(%)[b]	Yield 3(%)[b]	Yield 4(%)[b]
1[c]	BMPM	$FeCl_3$	1	10	61	16	11
2[c]	"	$Sc(OTf)_3$	1.5	25	44	22	6
3[c]	"	$InCl_3$	4	15	38	40	5
4[c]	"	AuCl	2.5	30	44	14	8
5[c]	"	$NaAuCl_4$	24	10	48	35	7
6	"	$CuBr_2$	4.5	0	53	47	0
7[c]	iPr	$FeCl_3$	7	15	30	16	4
8[c]	"	$Sc(OTf)_3$	6.5	10	36	18	6
9	"	$InCl_3$	5.5	10	58	18	11
10	"	AuCl	8	18	13	13	n.d.[d]
11[c]	"	$NaAuCl_4$	7	10	58	18	7
12	"	$Pd(MeCN)_2Cl_2$	72	90	0	0	10
13	**"**	**$CuBr_2$**	**4.5**	**0**	**64**	**24**	**0**
14	"	$CuBr_2$ THF	12	5	63	20	5
15	"	$CuBr_2$ dioxane	24	65	12	5	9
16	"	$CuBr_2$ DCE	24	35	38	8	12

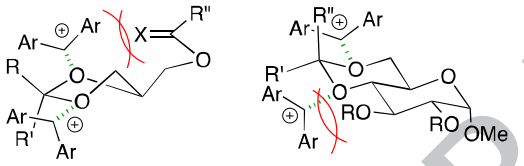
a) $[(BMPM)_2O]$= 1 M or [BMPM-O*i*Pr]= 1.1 M, [Acetal]= 1 M, $[Cu^{2+}]$= 0.1 M, in acetonitrile unless otherwise noted; b) Isolated yield, without taking into account conversion; c) dichloroethane as solvent; d) n.d. for not determined.

We first examined the role of the acetal nature in the outcome of this transformation, since it has been showed that ring and substituent sizes of acetal affect their hydrolysis.[22] A series of monopivaloyl glycerol, protected with acetals of various sizes, was prepared and engaged in the $CuBr_2$-catalyzed transprotection. Increasing the size, from dimethyl to diethyl, led to substantial decrease in reactivity, with a significantly lower conversion (~ 25%) and thus lower yields, but also in selectivity with an equal amount of mono and diBMPM ethers formed (entry 2 vs 1). Increasing rigidity with cyclohexylidene acetal also led to some decrease in reactivity and selectivity, but to a less extend (entry 3). Lowering the size did not increase reactivity nor selectivity (entries 4-5), while the simplest acetal seemed too fragile and only led to decomposition under the reaction conditions (entry 6). Surprisingly,

shifting from 1,3-dioxolane to 1,3-dioxane restored reactivity and seemed to increase the selectivity, but in favor of the diBMPM ether (entry 7 vs 5).

To check the latter point and to invert the reaction course, we investigated the reactivity of benzylidene acetals and acetonide derived from carbohydrates (entries 9-11). It is worth noting that such compounds already exhibit an acetal moiety, potentially leading to competition and opening of the carbohydrate ring. Rewardingly, not only the carbohydrate moiety was preserved but the regioselectivity of the acetal opening was very good and even excellent starting from acetonides. Mostly or almost exclusively was the 6-*O*-monoBMPM product formed, as expected from steric constrain in such 4,6-*O*-benzylidene acetal derived from glucose (entry 11 *vs* 9, 10).

From these results, we can confirm the proposed mechanism (see Scheme 2). Copper(II) bromide acts as Lewis acid and, upon coordination to the BMPM reagent, provides dimethoxybenzhydryl carbocation and a cuprate, The carbocation could then be trapped by the oxygen atom of the acetal, leading to acetal opening and ultimately to transprotection. Such mechanism also allows to explain the regioselectivity usually observed, based on steric grounds (Scheme 4).



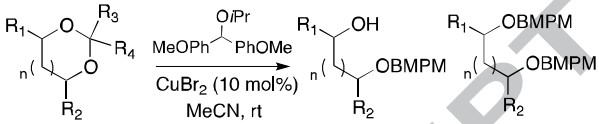
Scheme 4. Rational for the observed regioselectivity in the present Cu^{II}-catalyzed transprotection of acetals.

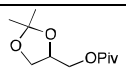
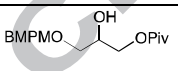
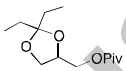
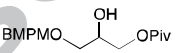
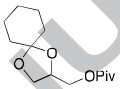
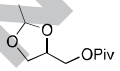
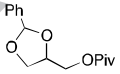
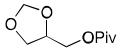
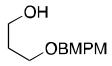
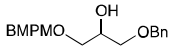
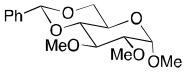
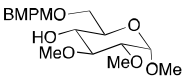
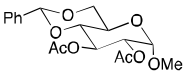
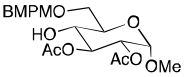
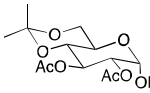
In summary, we have showed that transprotection of acetals to bis(methoxyphenyl)methyl (BMPM) ethers can be efficiently achieved in the presence of copper dibromide as catalyst at room temperature. Starting from disymmetric acetals, the reaction mostly provides the monoBMPM ether. Furthermore, the reaction is regioselective, producing the less crowdy monoBMPM ether. The reaction conditions are also very mild and tolerant to various functional groups, including other protecting groups.

Copper(II) salts are cheap and non toxic Lewis acids; it is thus worth to develop new applications of copper salts in organic synthesis.[23] The present interconversion of acetals to BMPM ethers offers a new tool to the chemist palette.

Further works are now in progress to further explore the scope of this reaction and to extend its application to organic synthesis.

Table 3. Screening of conditions for the acetal to BMPM ether interconversion.[a]



Entry	Acetal	mono BMPM	Time (h)	Yield (%)[b] mono:di
1			4.5	88 3:1
2			4	70[c] 1:1
3		"	5	78 2:1
4		"	9	75[c] 1.5:1
5		"	9	50[d] 1.5:1
6		"	24	traces[e] -
7			6	61[c] 1:4
8			7	75 1.4:1
9			7	55[c] 6:1
10			7	51[c] 6:1
11		"	4.5	40[d] 19:1
			4	52[f] 42:1

a) [BMPM-OR]= 1.1 M, [Acetal]= 1 M, [Cu^{2+}]= 0.1 M; b) Isolated yield; c) 15-25% of starting material recovered; d) 30% of starting material recovered; e) degradation occurred; f) performed in THF.

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Typical procedure: To a solution of acetal (1 mmol) and BMPMOiPr (316 mg, 1.1 mmol) in dry acetonitrile (1 mL) was added in one portion dried copper dibromide (22.5 mg, 0.1 mmol). The resulting green solution was magnetically stirred under argon at room temperature for 4.5 hours. The reaction mixture was concentrated under vacuum and then diluted with ether (15 mL) and water (15 mL). After partitioning, the aqueous layer was extracted three times with ether (15 mL) and the combined organic layers were dried over Na_2SO_4. After ether evaporation, the residue was then purified by flash chromatography over silica gel.