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Benzylsulfonyl: a valuable protecting and deactivating group in phenol chemistry

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Abstract—We introduce benzylsulfonyl (Bns) as a valuable protecting group in phenol chemistry. Bns proved to be stable under drastic reaction conditions and towards many common reagents. The deprotection proceeds quantitatively using catalytic hydrogenolysis. Additionally the Bns deactivating properties make this protecting group useful for tuning the reactivity of phenolic substrates.

Protecting groups not only temporarily block reactive sites but they also modify the intrinsic reactivity of the substrates.[1] Usually this side effect is considered by the chemist as a negative aspect of protecting group strategies. However, sometimes, the reactivity alteration induced by the protecting group becomes synthetically useful. As an example, Trost reported a lithiation of a trioxygenated benzene by inhibiting the *ortho* directing effect of an oxygen substituent when introducing a *t*-butyldimethylsilyl protection.[2] Also, we have recently shown that the regioselectivity of aromatic electrophilic substitution can be inverted by converting a phenol group into its methanesulfonate derivative. Indeed, the strong electron withdrawing effect of sulfonyl residue neutralizes the phenol *ortho*/*para* directing effect.[3] The use of 'Not-so-innocent bystanders' protecting groups, as stated by Kocienski,[4] to affect and influence the outcome of a reaction, provides novel synthetic opportunities.

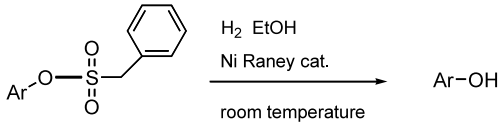
The 'deactivating' properties of sulfonic esters would be very useful in polyphenol chemistry since it would enhance the stability of the various intermediates. However, we and others[5] have observed that conditions for deprotection of aromatic methanesulfonic esters are not compatible with polyphenol skeletons.

Until now, because of the mildness of hydrogenolytic cleavage, benzyl-type ethers are among the most frequently encountered protecting groups in polyphenol chemistry.

Therefore, we searched for a phenol protecting group that would combine both deactivating properties and mild hydrogenolysis cleavage feature. An interesting candidate appeared to be the benzylsulfonyl (Bns) group. Although Bns has only been rarely reported in the literature[6] it is readily introduced, using inexpensive commercially available benzylsulfonyl chloride in the presence of triethylamine or pyridine. Surprisingly, no mild deprotection method has been described.

Herein we describe the reactivity chart of Bns esters. We show that while stable under acidic and basic conditions, Bns can be readily cleaved under an hydrogen atmosphere using catalytic Raney Nickel (Scheme 1). Moreover, Bns exhibits the same deactivating properties as its methanesulfonic parent.

To evaluate the scope and the limitations of the Bns as a phenol protecting group and to define a reactivity chart, a model compound (ArOH = 4-ethylphenol) was



Scheme 1. General scheme for catalytic hydrogenolysis of benzylsulfonyl protecting groups (Bns).

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subjected to a range of chemical conditions (Table 1). We tested various media derived from prototype reagents given by Greene in his reactivity charts.[1]

Table 1. Reactivity chart for benzylsulfonyl protecting group[b]

Conditions	Reactivity	
H_2, Ni Raney (50%water)	**R**	Catalytic hydrogenolysis[a]
H_2, Ni on silica-alumina 48 h	**S**	
H_2, Pd/ activated carbon (10% Pd) 48 h	**S**	
H_2, Pd on $BaSO_4$ (5% Pd) 48 h	**S**	
H_2, Pd on $CaCO_3$ (5% Pd) 48 h	**S**	
H_2, Lindlar catalyst (5% Pd with 3.5% Pb) 48 h	**S**	
H_2, Pd hydroxide on carbon (20% Pd) 48 h	**S**	
H_2, Ru on carbon (5% Ru) 48 h	**S**	
H_2, Pt/activated carbon (10% Pt) 48 h	**S**	
H_2, Rh on alumina (0.5% Rh) 48 h	**S**	
H_2, Rh on carbon (5% Rh) 48 h	**S**	
HCl 1.2N, EtOH/H_2O 0.15M, 48 h, RT	**S**	Acidic media
HCl 1.2N, EtOH/H_2O 0.15M, 4 h, 100°C	**S**	
H_2SO_4/AcOH 2/3, 6 h, 80°C	**S**	
$AlCl_3$, THF 0.15M, 48 h, RT	**S**	
NaOH 1.2N, EtOH/H_2O 0.15M, 48 h, RT	See text	Basic media
NaOH 1.2N, EtOH/H_2O 0.15M, 4 h, 150°C	**R**	
KOH, MeOH 0.4 M, 24 h, RT	**R**	
K_2CO_3, MeOH 0.15M, 48 h, RT	See text	
NEt_3 0.15M, 48 h, RT	**S**	
Pyridine 0.15M, 48 h, RT	**S**	
t-BuOK, THF [8]	**U**	Nucleophile
RLi, THF, -78°C	**U**	
RMgX	**S**[c]	
Zn/AcOH 0.15M, 48 h, RT	**S**	Redox media
$NaBH_4$ [9]	**S**	
$LiAlH_4$, THF 0.15 M	**U**	
MnO_2, benzene 0.15M, 48 h	**S**	
$KMnO_4$, acetone/H_2O 0.15M , 0°C, pH 7	**S**	
m-CPBA, CH_2Cl_2 0.15M, 0°C	**S**	

[a] Hydrogenation are conducted with 10% catalyst in EtOH 0.04 M at room temperature.

[b] Reactivity is classified in three levels:
– **S**(**S**table) indicates that the protective group is stable under the corresponding conditions, 100% of the starting material is recovered.
– **R**(**R**emoved) indicates that the protective group is removed quantitatively to give the deprotected phenol.
– **U**(**U**nstable) indicates that neither the protected product nor the deprotected phenol are recovered.

[c] The stability of the Bns group depends on the reaction conditions as described below.

First we noticed that the Bns group is specifically removed under hydrogen with Raney Nickel, while it proves to be inert under various other catalytic hydrogenation conditions (Pd/C, Lindlar catalyst, Rh/C…). Interestingly the Bns and benzyl groups appear orthogonally stable to each other.

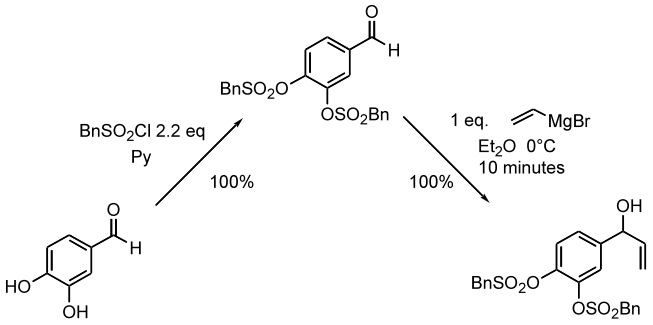
The Bns group is cleaved by some basic media but remains stable to classic organic bases at room temperature. Indeed relative rates have to be taken into account when using basic conditions as only partial cleavage could be observed. With NaOH 1.2N in EtOH/H_2O or with K_2CO_3 in MeOH, we only observed 15% of deprotected product after 48 h at room temperature. Otherwise this protecting group exhibits high stability under acidic conditions even at high temperatures. Various sets of conditions were tested, namely media typically involved in electrophilic aromatic substitution processes (H_2SO_4, AcOH 2/3 under heating). An illustrative amidomethylation of benzylsulfonylguaiacol is reported below.

With organometallic reagents, the stability of the benzylsulfonyl functionality depends on the reaction conditions. They should be determined experimentally as shown in the vinylation with Grignard reagents, which proceeds quantitatively in diethyl ether but affords more than 20% by-products in THF (Scheme 2). Organolithium compounds proved to be incompatible and with *t*-butoxide potassium, α-sulfonylation of the sulfonic ester has been reported.[7]

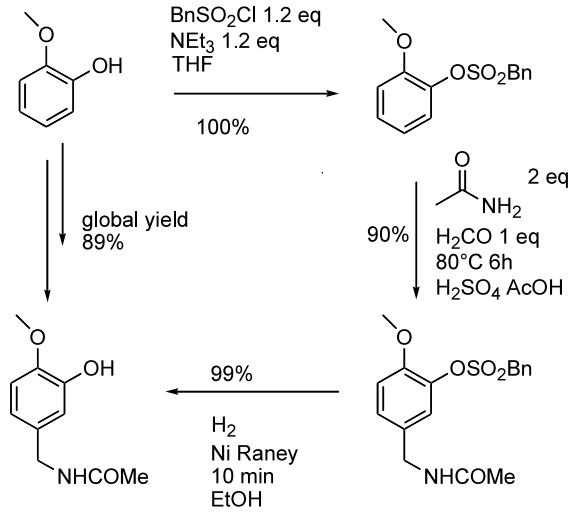
Under mild reductive conditions ($NaBH_4$) the Bns group is not affected, allowing, as reported, selective ketone reduction on steroid structures.[8]

Among other characteristics of the Bns group, its electron withdrawing character has to be emphasized. As previously reported, isoguaiacol derivatives could be obtained by derivatization of guaiacol as a methanesulfonic ester. Now we report the advantageous replacement of the mesyl group by the Bns. Indeed, Bns provides milder deprotection conditions while enabling identical regiochemical control (Scheme 3).

Benzylsulfonylguaiacol subjected to 2 equiv. of acetamide, 1 equiv. of aldehyde at 80°C for 6 h in a mixture



Scheme 2. Vinylation with Grignard reagents.



Scheme 3. Amidomethylation.

2:3 sulfuric acid/acetic acid mixture, leads regioselectively to 90% of the desired 5-substituted guaiacol. Removal of the Bns group is then achieved by stirring under hydrogen atmosphere in ethanol with 10% Raney Nickel. After 10 min the free phenol is obtained in 99% yield. The amidomethyl moiety remains unaffected (Scheme 3).

In summary, Bns proved to be stable under drastic conditions and towards many common reagents. The subsequent deprotection proceeds almost quantitatively using catalytic hydrogenolysis.[9] These results enlarge the available methods in protecting group chemistry. Additionally deactivating properties of Bns make this protecting group useful for tuning the reactivity of phenolic substrates. These properties open new perspectives in polyphenol chemistry. Investigations in total synthesis of natural products are underway.

Acknowledgements

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9. **Caution**: Raney Nickel should never be allowed to dry. Experimental: To a solution of 4-ethylphenol benzylsulfonyl ester (80 mg) in ethanol (4 mL) is added Raney Nickel (8 mg, 10% of the mass). The mixture is then degassed and stirred under an hydrogen atmosphere at room temperature. The reaction is monitored by TLC. Subsequent work-up of the reaction consists of filtration through Celite.