New Applications of 1,5-Hydrogen Atom Transfer Reactions: Self-Oxidizing Protecting Groups

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Three new alcohol protecting groups are introduced: α-bromobenzyl, α-bromo(methylenedioxy)benzyl, and α-bromotriethyl. Removal of these protecting groups under reductive conditions with tributyltin hydride is coupled with an oxidation of the substrate to produce directly an aldehyde or ketone. This oxidation occurs by 1,5-hydrogen transfer, followed by β-fragmentation. For example, treatment of the α-bromobenzyl ether of 3-phenyl-1-propanol with tributyltin hydride at 0.001 M (80 °C) directly produces 3-phenyl-1-propanol. An application to the selective oxidation of primary alcohols in the presence of secondary alcohols is also introduced.

The protection of functional groups² and the interconversion of functional groups by reduction or oxidation are two fundamental synthetic tactics that are rarely coupled. A sequence of protection and deprotection almost always leaves a functional group in the same oxidation state after deprotection as before. However, it is not uncommon to carry a functional group through a synthetic sequence in a different oxidation state from that which is ultimately required. For example, aldehydes and ketones are often carried as protected alcohols. To convert the protected functional groups to the required end products, two steps – deprotection and oxidation (or reduction) – are usually required. It would be desirable to have a suite of protecting groups which, when removed, directly formed products in a higher (or lower) oxidation state than the precursors.

We now introduce the first members of a new class of protecting groups. These protecting groups are installed at the alcohol oxidation state. Their removal under mild conditions is coupled with an oxidation of the substrate to an aldehyde or ketone, hence the name “self-oxidizing protecting groups”. This class of reagents also has use beyond the field of protecting group chemistry for conducting selective oxidations. Most significantly, the oxidations occur under conditions that are traditionally considered as mildly reductive (Bu₃SnH), and thus the chemoselectivities observed are completely unrelated to the ease of oxidation of the functional groups in a given substrate.

The basic concept is outlined in Scheme 1. 3-Phenyl-1-propanol is “protected” by O-alkylation with α-bromobenzyl bromide (1a).³ The resulting α-bromobenzyl ether 2a is a variant of a standard benzyl ether, and we have previously used this modified benzyl ether to conduct sequences of radical translocation/cyclization.⁴ In the case at hand, direct “deprotection” of 2a was accomplished by reduction with tributyltin hydride at 0.001 M. This formed 3-phenylpropanol (3) and the benzyl ether 4 in a ratio of about 5:1. The 2,4-dinitrophenyl hydrzone derivative 5² of 3-phenylpropanol was isolated in 66% yield.

A probable sequence for formation of 3 is readily formulated, as outlined in Scheme 2. Initial bromine abstraction is followed by 1,5-hydrogen transfer⁶ from aryl radical 6 to give α-alkoxy radical 7. Fragmentation⁷ of 7 gives aldehyde 3 and the benzyl radical, which presumably abstracts hydrogen from tributyltin hydride⁸ to form toluene and continue the chain. Each of these steps is a well-known radical reaction. The combination couples the removal of the α-bromobenzyl protecting group with oxidation of the substrate from an alcohol to an aldehyde. The use of low tin hydride concentrations is critical since trapping of either radical 6 or radical 7 by hydrogen transfer derailed the sequence by forming 4.

We have conducted a similar sequence of reactions starting with the methylenedioxy analog 2b (Scheme 1),
Scheme 3

and slightly better yields of 5 are obtained in the deprotection step. However, the o-bromo(methylenedioxy)benzyl bromide is a more reactive alkylating agent, and better yields are also obtained in the protection step. The yield differences in the protection step are even larger for secondary alcohols, as shown in Scheme 3. Both cis- and trans-4-tert-butylcyclohexanol were “protected” with 1a and 1b, and then “deprotected” to give the dinitrophenyl hydrazide derivative 10. Protection steps proceeded with better efficiency in the b series, but deprotection yields were all comparable. Only traces of the directly reduced benzyl ethers were formed when the tin hydride reduction was conducted at 0.005 M. Taken together with the previous results, this means that most of the reduced, debrominated products in Scheme 2 probably resulted from failed 1,5-hydrogen transfer (6 → 7) and not failed fragmentation (7 → 3).

We envision that these protecting groups and others like them can be useful in complex synthesis. Only the functionality bearing the protecting group is targeted for oxidation, and even that oxidation is accomplished under reductive conditions. This analysis suggests a second application of such groups for selective oxidation. The ability to selectively oxidize a given alcohol in a polyol would be determined by its ease of derivatization rather than its ease of oxidation.

To implement this idea, we prepared o-bromotrityl chloride (11) as a variant of the standard trityl protecting group (Scheme 4). Tritylation of 3-phenyl-1-propanol gave 12 in 52% yield. Reduction of 12 with tin hydride and subsequent hydrazide formation produced DNP derivative 5 in 83% yield. Next, we demonstrated the possibilities for selective oxidation of a diol. As expected, tritylation with 11 was selective for the primary hydroxy group, and only monotrityl derivative 14 was formed from 13. Reduction of 14 with tin hydride produced the sensitive hydroxy aldehyde 15 in 56% yield. Overall, a selective oxidation of a primary hydroxy group in the presence of an unprotected secondary allylic hydroxy group was accomplished. This very difficult transformation is usually orchestrated by juggling different protecting groups on primary and secondary alcohols.

Another variant on the theme couples the introduction of the protecting group with a standard C–C bond forming reaction. Scheme 5 illustrates this concept by using the Mukaiyama aldol reaction of 16 with 17 to give 18 as a mixture of diastereomers. Reduction of 18

Scheme 4

Scheme 5
with tin hydride was not an especially clean reaction, but we were able to isolate 19 in 35% yield. The GC yield of 19 was 18%.

These simple examples suffice to illustrate that self-oxidizing protecting groups should facilitate the execution of complex synthetic sequences in many different ways. We have introduced three such groups (o-bromobenzyl, o-bromo(methylenedioxy)benzyl, and o-bromotrityl), and it should certainly be possible to develop new members of the class. However, we caution that the scope of these reactions is not yet well established. As yet, we have made no effort to optimize conditions in either the protection or deprotection steps. Further, relatively little is known about substituent effects on 1,5-hydrogen transfer reactions from C–H bonds to carbon-centered radicals, and this is an especially vulnerable step. Fragmentation reactions of α-alkoxyalkyl radicals have also not been studied in complex systems. For the moment, we recommend that appropriate model studies should precede the attempted application of these or related groups in complex synthetic problems.

1-(2-Bromophenyl)-5-phenyl-2-oxapentane (2a): A solution of 2a (4.40 mmol, 0.5 mL), 60% NaH (4.40 mmol, 176 mg) and 3-phenyl-1-propanol (3.67 mmol, 300 mg) in THF (40 mL) was refluxed for 0.5 h. After cooling to 0°C, 2-bromobenzyl bromide (3.74 mmol, 368 mg) and Bu$_3$N (0.37 mmol, 24 mL) were added, and the mixture refluxed for 16 h. The turbid solution was filtered, diluted with EtO$_2$ (50 mL), washed with water and brine, dried (MgSO$_4$), and concentrated. The crude product was isolated by flash column chromatography (EtOAc/hexane = 1:1) to give 2a (57%, 638 mg) as a colorless oil.

1H NMR (300 MHz, CDCl$_3$), δ = 7.55–7.14 (9 H, m), 4.56 (2 H, s), 3.57 (2 H, t, J = 6.3 Hz), 2.75 (2 H, t, J = 7.4 Hz), 1.98 (2 H, quint., J = 6.3 Hz).

13C NMR (75 MHz, CDCl$_3$), δ = 141.92, 137.94, 132.47, 128.89, 128.82, 128.53, 128.39, 127.37, 125.81, 122.64, 72.14, 70.00, 32.41, 31.38.

IR (neat): ν = 3026, 2939, 2860, 1105, 1124 cm$^{-1}$.

M/z: m/z = 306 (M + 2), 304 (M), 288, 245, 207, 185, 169, 118, 91 (base peak).

HRMS for C$_{16}$H$_{12}$Br$_2$O calced 368.0987, found 368.0987.

trans-(2-Bromobenzoxy)-4-tert-butylicyclohexane (9a): Compound 9a was prepared following the procedure for 2a with DMPU (2.64 mmol, 0.32 mL), 60% NaH (2.64 mmol, 106 mg), 3-phenyl-1-propanol (2.2 mol, 300 mg), 6-bromophenylpiperidinone (2.64 mmol, 777 mg), and Bu$_3$N (0.22 mmol, 81 mg) in THF (20 mL). Purification by flash column chromatography (EtOAc/hexane = 1:1) gave 2b (68%, 322 mg) as a colorless oil.

1H NMR (300 MHz, CDCl$_3$), δ = 7.52–7.08 (4 H, m), 4.60 (2 H, s), 3.30 (1 H, m), 2.19–2.15 (2 H, m), 1.83–1.60 (2 H, m), 1.30–0.97 (5 H, m), 0.85 (9 H, s).

13C NMR (75 MHz, CDCl$_3$), δ = 138.59, 133.96, 132.60, 129.08, 127.97, 126.64, 78.81, 69.36, 47.49, 47.32, 36.10, 32.80, 27.22, 25.68.

IR (neat): ν = 2945, 2862, 1095, 1026 cm$^{-1}$.

M/z: m/z = 326 (M + 2), 324 (M), 267, 249, 227, 225, 171, 169 (base peak), 138, 57.

HRMS for C$_{16}$H$_{12}$Br$_2$O calced 324.1089, found 324.1089.
\(^1\)H NMR (300 MHz, CDCl\(_3\); \(\delta = 9.76 - 9.63\) (1 H, m), 6.12 - 5.53 (2 H, m), 4.65 - 4.18 (1 H, m), 2.79 - 0.84 (6 H, m).

\(^1\)C NMR (75 MHz, CDCl\(_3\); \(\delta = 204.16, 203.45, 131.46, 130.76, 128.72, 127.59, 127.30, 126.78, 103.15, 72.40, 65.08, 62.76, 44.83, 42.15, 41.06, 31.30, 24.39, 23.76.

IR (neat): \(\nu = 3397, 3030, 2922, 2729, 1716, 1651, 1526\) cm\(^{-1}\).

MS: \(m/z = 225\) (M\(^+\), 113, 108, 97, 79 (base peak), 69, 55.

HRMS for C\(_{24}\)H\(_{30}\)BrO\(_2\) calcld 368.0987, found 368.0987.

4-tert-Butylcyclohexanone 2',4'-Dinitrophenylhydrazone (10):

Compound 10 was prepared following the procedure for 5 with the appropriate precursor (8a, 8b, 9a, or 9b, 0.276 mmol). Bu\(_3\)SnH (0.331 mmol, 89 \µL), and AIBN (0.027 mmol, 4.4 mg) in benzene (0.055 M, 55 mL) to give the product 10 (73% from 8a, 82% from 8b, 79% from 9a, and 89% from 9b) as a yellow solid (mp 151 - 152°C).

IR (CH\(_2\)Cl\(_2\); \(\nu = 3397, 3030, 2922, 2729, 1651, 1556, 1567, 1385, 1261\) cm\(^{-1}\).

1,2-Dibromo-1,1,1-triethyl-2-oxapentane (12):

A solution of 1,2-dibromo-1,1,1-triethyl-2-oxapentane (1.03 mmol, 370 mg) and 3-phenyl-1-propanol (0.734 mmol, 0.10 mL) in DMF (10 mL) was cooled to 0°C and added to Et\(_3\)N (2.20 mmol, 0.27 mL) and DMAP (0.073 mmol, 9 mg), and allowed to warm to 25°C. After 20 h at 25°C, the mixture was diluted with Et\(_2\)O (50 mL), washed with aq NH\(_4\)Cl and brine, dried (MgSO\(_4\)), and concentrated. Flash column chromatography (EtOAc/hexane = 1:1) of the residue gave 12 (52%, 174 mg) as a pale green oil.

IR (CH\(_2\)Cl\(_2\): \(\nu \approx 3030, 2922, 1716, 1196, 1051\) cm\(^{-1}\).

MS: \(m/z = 326\) (M + 2), 324 (M), 282, 280, 215, 213, 171, 169 (base peak), 140, 90, 83.

HRMS for C\(_{24}\)H\(_{30}\)BrO (M - CH\(_2\)CO) calcld 282.0619, found 282.0619.

2-Acetyl-2-methylcyclohexanone (19):

Compound 19 was prepared following the procedure for 5 with \(18\) (0.461 mmol, 150 mg), Bu\(_3\)SnH (0.532 mmol, 171 \µL) and AIBN (0.046 mmol, 7.57 mg) in benzene (93 mL). Purification by flash column chromatography (EtOAc/hexane = 1:1) gave 19 (29 mg, 35% isolated, 48% GC) as a colorless oil.

IR (neat): \(\nu = 2922, 2714, 1651, 1435\).

MS: \(m/z = 154\) (M\(^+\), 139, 126, 112 (base peak), 97, 84, 69, 59, 55, 43.

HRMS for C\(_{14}\)H\(_{20}\)O\(_2\) calcld 154.0994, found 154.0994.

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(13) The 1H-NMR spectrum of the crude reaction mixture indicated that 15 was formed in a good state of purity. However, after chromatography a mixture of compounds was formed which contained 15 (major) along with what we suspect are the epimerized aldehyde and the epimeric lactols. This same mixture was generated by reduction of the following lactone.

(14) A typical sequence is as follows: 1) protect 1'-OH with Group A; 2) protect 2'-OH with Group B; 3) remove Group A; 4) oxidize 1'-OH; 5) remove Group B.