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Radical-mediated intramolecular C–C bond formation and the deoxygenation of alcohols under solvent-free conditions with tributyl methyl ammonium hypophosphite

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ABSTRACT

A green, solvent-free protocol was developed for the radical-mediated intramolecular cyclization of haloacetals and the deoxygenation of *S*-methyl dithiocarbonates and cyclic thionocarbonate. This process uses tributyl methyl ammonium hypophosphite as a H-donor in the presence of triethylborane or *t*-butyl peroxide. This methodology provides eco-friendly reaction conditions.

Free radical reactions[1] represent a ubiquitous class of synthetic reactions that are traditionally performed in organic solvents. Recently, efforts have been made to avoid highly volatile, environmentally hazardous, and biologically incompatible organic solvents for radical reactions. Research in this area has investigated the use of ionic liquids, supercritical carbon dioxide, and fluorous solvents.[2] However, because of its cost, availability, and eco-friendly nature, water remains an obvious choice for replacing organic solvents.[3] In green chemistry, the reduced use of solvents is of paramount significance.[4] In effect, 'the best solvent is no solvent.[5] Solvent-free radical polymerization reactions are well documented in the literature.[6] Except for a few isolated examples,[7] however, the use of such methodology in free radical-based organic synthesis is scarcely investigated. There is a great need to develop protocols for free radical reactions in the absence of solvent.

Phosphorous hydrides offer a viable alternative to organotin hydrides.[8] Tetraalkylammonium hypophosphites (THAPs) have received much attention because they are economic, mild, and known to readily generate radicals from alkyl halides.[9] In addition, they act as surfactants, increasing the solubility of organic compounds.[10] Previously, we reported the utility of various THAPs for the radical deoxygenation of alcohols and the formation of carbon–hydrogen bonds in aqueous media without additives.[11] Of the THAPs developed, tributyl methyl ammonium hypophosphite (TBMAP) was found to be an extremely useful hydride because it exists in crystalline form at room temperature. This property allows easy handling while its slight solubility in water facilitates effortless synthesis, isolation, and purification. Due to concerns of environmental pollution from the extensive use of volatile organic solvents, we aimed to demonstrate radical-based reactions under neat conditions using TBMAP.

Intramolecular radical cyclizations in solvents and aqueous media are now well known.[1,12] Due to ecological concerns, however, the development of an efficient synthetic methodology for accomplishing these reactions under solvent-free conditions is of considerable importance. We present here the intramolecular radical cyclization of haloacetals in solvent-free conditions using TBMAP as a H-donor.

First, we studied the cyclization of various haloacetals, **1a–f**, in the presence of 5 equiv of TBMAP and 0.25 equiv of triethylborane. At 60 °C and in neat conditions, this resulted in the cyclic products **2a–c** (Table 1).[13] The inherent reactivity of haloacetals varied and was controlled by the nature of the substrate. 3-Iodo-2-(3-methyl-2-propenyloxy)tetrahydropyran (entry 1) and 2-(hex-2-enyoxy)-3-iodotetrahydro-2*H*-pyran (entry 3) reacted readily compared to 2-(cinnamyloxy)-3-iodotetrahydro-2*H*-pyran (entry 5). The phenyl ring of the latter substance might have hindered radical cyclization and caused the low yield of **2c**. Bromo-derivatives underwent cyclization quite slowly compared to the corresponding iodo-derivatives (entries 2, 4, and 6), proving that the iodo-group is easily abstracted by an TBMAP radical.

Mechanistically, this solvent-free radical cyclization proceeds in the presence of triethylborane/oxygen via the initial generation of

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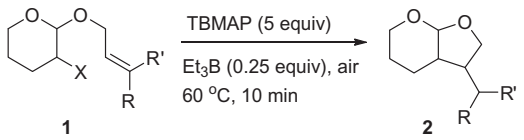
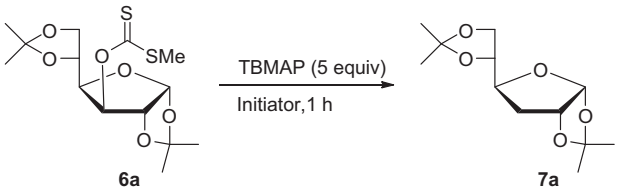
Table 1
Intramolecular radical cyclization of haloacetals **1**



Entry	Substrate	X	R	R′	Product	Yield (%)[a]
1	**1a**	I	Me	Me	**2a**	90
2	**1b**	Br	Me	Me	**2a**	58
3	**1c**	I	*n*-Pr	H	**2b**	93
4	**1d**	Br	*n*-Pr	H	**2b**	85
5	**1e**	I	Ph	H	**2c**	31
6	**1f**	Br	Ph	H	**2c**	11

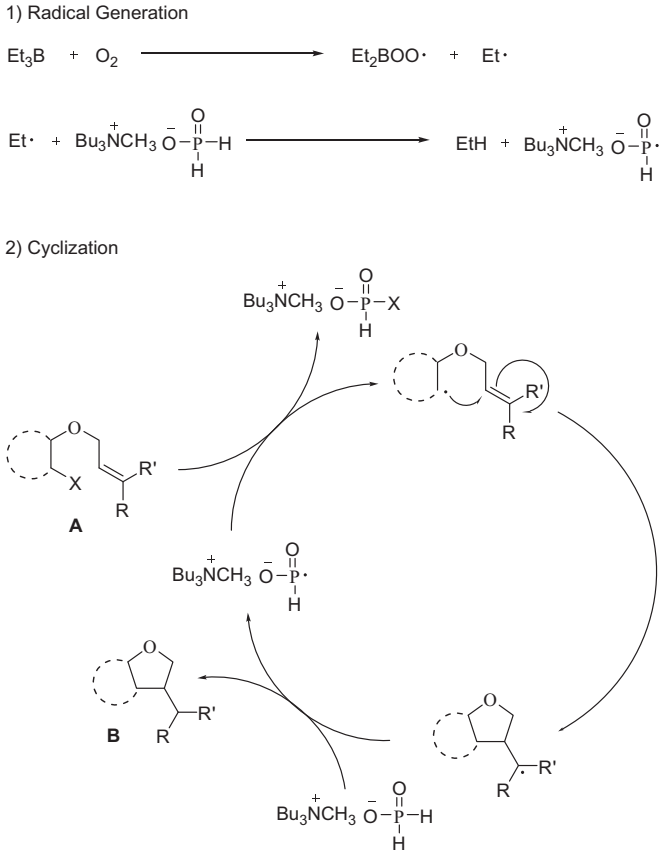
[a] Isolated yield.

Table 2
Deoxygenation of *S*-methyl dithiocarbonate **6a** under various reaction conditions



Entry	Initiator (equiv)[a]	Temp (°C)	Yield (%)[b]
1	Et_3B (0.25)	60	62
2	Et_3B (1)	60	44
3	Et_3B (3)	80	64
4	Et_3B (2)	100	65
5	$(^tBuO)_2$ (0.25)	100	81
6	$(^tBuO)_2$ (0.5)	100	74
7	$(^tBuO)_2$ (0.75)	100	68

[a] A needle was inserted through a rubber septum for an air inlet when Et_3B was used as initiator.
[b] Isolated yield.



Scheme 1. Mechanistic pathway for the cyclization of haloacetals.

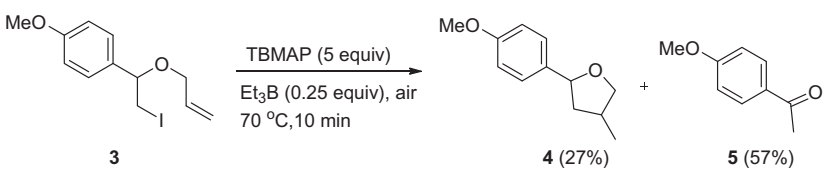
a phosphorous radical. The phosphorous radical then abstracts a halogen from haloacetal **A** and the subsequent C–C bond formation (of acetal radical) results in product **B** (Scheme 1).

Next, the cyclization of 1-(1-(allyloxy)-2-iodoethyl)-4-methoxybenzene (**3**) was performed under the reaction conditions and the desired product **4** was formed. However, product **4** had a minor yield with 4-methoxy acetophenone (**5**) as a major by-product (Scheme 2). Due to its hydrophobic nature, most of the starting material may have not participated in the reaction. Instead it decomposed, resulting in compound **5**.

To evaluate optimized conditions, the radical deoxygenation of alcohols using *S*-methyl dithionocarbonate **6a** as a test substrate was investigated (Table 2). Deoxygenation with triethylborane gave moderate yields even at elevated temperatures (entries 1–4). However, using 0.25 equiv of *t*-butyl peroxide at 100 °C gave **7a** in high yield (entry 5).[14] Efforts to increase the yield of **7a** with excess initiator were futile (entries 6 and 7). The deoxygenation of various *S*-methyl dithiocarbonates has been performed using 0.25 equiv of $(^tBuO)_2$ at 100 °C (Table 3). Both primary and secondary dithiocarbonates reacted smoothly and gave products in respectable yields (entries 1–3). The rate of deoxygenation was found to be faster without solvent than it was in water and yields were comparable.[11]

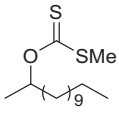
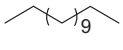
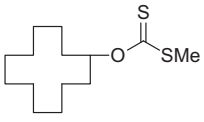
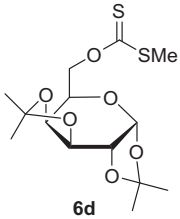
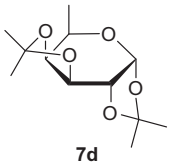
The reaction of the cyclic thionocarbonate of (*R*,*R*)-tartarate **8** under solvent-free conditions was examined (Table 4). After considerable experimentation, it was found that the optimal conditions used 1 equiv of Et_3B at 60 °C for 4 h to give product **9** in 63% yield (entry 6).

In conclusion, we have developed an efficient, eco-friendly, and neat strategy for the radical-promoted C–C bond formation of haloacetals and the deoxygenation of *S*-methyl dithiocarbonates and cyclic thionocarbonates. This method uses tributyl methyl ammonium hypophosphite. Reaction temperatures and the type of radical initiator were critical factors for these radical-mediated reactions in the absence of solvent. Deoxygenation proceeds faster in solvent-free conditions. These reactions are clean and simple, and prove the immense potential of tetrasubstituted hypophosphite in green free radical chemistry.



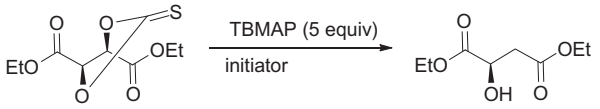
Scheme 2. Cyclization of substrate **3**.

Table 3
Deoxygenation of various *S*-methyl dithiocarbonates[a]

Entry	*S*-methyl dithiocarbonate	Product	Yield (%)[b]
1	 **6b**	 **7b**	82
2	 **6c**	 **7c**	73
3	 **6d**	 **7d**	77

[a] Reaction was performed using 0.25 equiv of $(^tBuO)_2$ at 100 °C.
[b] Isolated yield.

Table 4
Reaction of the cyclic thionocarbonate of (*R*,*R*)-tartarate under various reaction conditions



8 **9**

Entry	Initiator (equiv)[a]	Temp (°C)	Time (h)	Yield of **9** (%)[b]
1	$(^tBuO)_2$ (0.25)	100	0.5	35
2	$(^tBuO)_2$ (0.5)	100	1	38
3	Et_3B (0.25)	100	0.5	42
4	Et_3B (1.0)	60	1	43
5	Et_3B (1.0)	60	3	51
6	Et_3B (1.0)	60	4	63

[a] A needle was inserted through a rubber septum for an air inlet when Et_3B was used as initiator.
[b] Isolated yield.

Acknowledgment

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13. Typical procedure for intramolecular cyclization of haloacetals with TBMAP: A mixture of 3-iodo-2-(3-methylbut-2-enyloxy)tetrahydro-2*H*-pyran (**1a**) (236 mg, 0.80 mmol), TBMAP (1.07 g, 4.0 mmol) and Et_3B/air (0.20 mL, 0.20 mmol, 1 M solution in hexane) was heated at 60 °C for 10 min. After completion of reaction, mixture was diluted with CH_2Cl_2, then washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated the solvent in vacuo. The residue was purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 9:1) to furnish 3-isopropylhexahydro-2*H*-furo[2,3-b]pyran (**2a**) (122 mg, 90%).
14. Typical procedure for deoxygenation of alcohols with TBMAP: a mixture of 1,2:5,6-di-*O*-isopropylidene3-*O*-(methylthio)thiocarbonyl-α-D-glucofuranose (**6a**) (547 mg, 1.56 mmol), TBMAP (2.07 g, 7.81 mmol) and $(^tBuO)_2$ (71 μL, 0.39 mmol) was heated at 100 °C for 1 h. After completion of reaction, mixture was diluted with CH_2Cl_2, then washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated the solvent in vacuo. The residue was purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 7:3) to furnish 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**7a**) (309 mg, 81%).