Pergamon

Tetrahedron Letters 43 (2002) 5419–5422

TETRAHEDRON LETTERS

Single step transformation of PMB ethers to bromides using a CBr_4–TPP reagent system†

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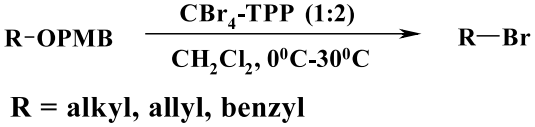
Received 8 April 2002; revised 29 May 2002; accepted 7 June 2002

Abstract—PMB ethers are efficiently transformed to their corresponding bromides by a CBr_4–TPP reagent system with a wide range of other functional groups also present in the substrate.

1. Introduction

Selective protection and deprotection of the hydroxyl functionality is an important process in multistep synthesis of complex natural products.[1] The direct conversion of a protected hydroxyl functionality to the corresponding bromide is also a desirable transformation in a multi-step synthesis as it increases the yield and efficiency of the synthesis. Among various hydroxyl protecting groups, the *p*-methoxybenzyl (PMB) ether is one of the most commonly used due to its stability towards a variety of reaction conditions and it can be selectively cleaved in the presence of benzyl ethers under mild conditions.

A combination of CBr_4 and triphenylphosphine (TPP) is a versatile reagent system used for various transformations.[2] Though the CBr_4–TPP reagent system has been employed for the conversion of THP and silyl ethers into their corresponding bromides, it has never been used for PMB ethers. In this communication, we report a novel, highly efficient and mild procedure for direct transformation of PMB ethers to bromides (Scheme 1). The reaction proceeds smoothly under mild conditions to afford high yields of alkyl bromides in a single step.



Scheme 1.

2. Results and discussion

The scope and generality of this process is illustrated with several examples and the results are summarized in Table 1. During the course of our studies directed towards the total synthesis of strongylodiols,[3a,3b] a new class of long chain acetylenic alcohols recently isolated by Iguchi et al.[3c] from a marine sponge of the genus *Strongylophora*, we needed to synthesize acetylene **2** from aldehyde **1** employing Corey's CBr_4–TPP reagent system aiming to get the dibromoolefin **3** then, by elimination with *n*-BuLi, the acetylene **2** (Scheme 2).

However, the isolated product was the alkyl bromide **4** (Table 1, entry a), which is formed in situ from the PMB ether by the action of the CBr_4–TPP reagent system (Scheme 3). These results encouraged us to change the reaction conditions and hence instead of 2 equiv. of CBr_4 and 4 equiv. of TPP, we employed 1 equiv. of CBr_4 and 2 equiv. of TPP and found that the resultant product was bromide **5** (Table 1, entry b), in which the aldehyde functionality remained intact (Scheme 4). The molar ratio was further changed to 1:1 but still it was found that the isolated product was bromide **5** albeit requiring a longer reaction time.

An extensive literature survey revealed that though different methods are available for selective cleavage of PMB ethers,[4] no report described PMB ethers being

Keywords: PMB ethers; strongylodiols; carbon tetrabromide; alkyl bromide; stereogenic center; chemoselective.

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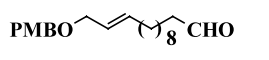
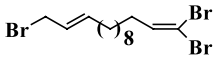
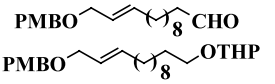
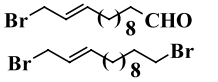
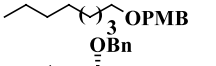
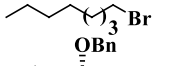
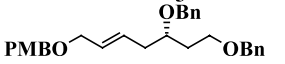
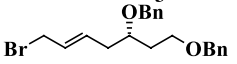
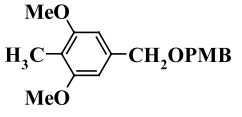
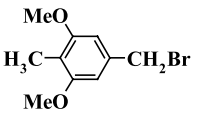
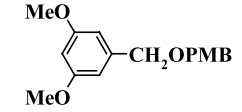
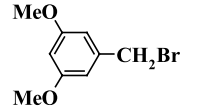
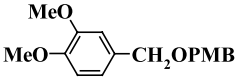
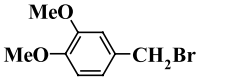
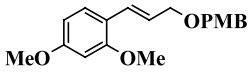
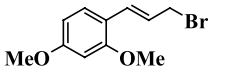
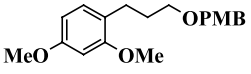
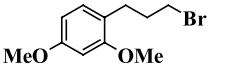
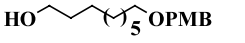
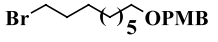
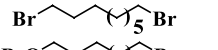
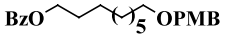
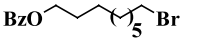
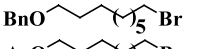
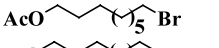
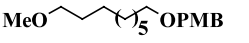
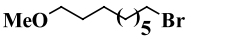
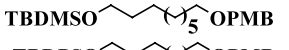
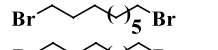
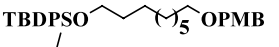
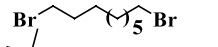
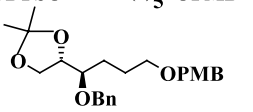
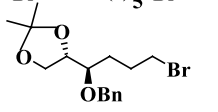
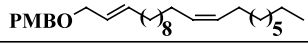
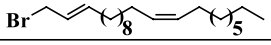
† IICT Communication No: 020111.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01068-7

Table 1. Single step transformation of PMB ethers to bromides using CBr_4–TPP reagent system

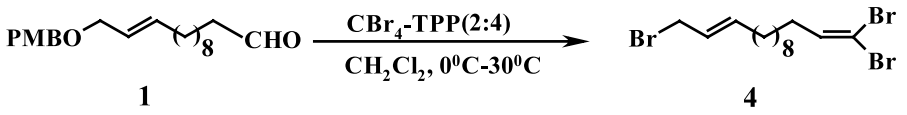
Entry	Substrate	Product[a]	Reaction Time (h)	Yield %[b]
a			0.5	92[c]
b			0.5	90
c			0.5	88[c]
d			2.5	85
e			0.5	90
f			1.5	45[d]
g			1.5	48[d]
h			1.5	52[d]
i			0.5	94
j			2.0	85
k			2.0	82
l			1.5	80[c]
m			2.5	84
n			3.0	85
o			2.5	80
p			3.5	85
q			2.0	85[c]
r			2.0	82[c]
s			3.0	85
t			1.0	90

a. All products were characterized by IR, NMR and mass spectroscopy
b. Isolated yields after column chromatography
c. 2:4 (CBr_4:TPP) was used for the transformation
d. *p*-methoxybenzyl bromide is also formed

Scheme 2.

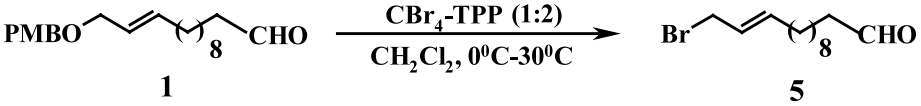
converted into bromides in a single step. Prompted by this serendipitous discovery, we decided to extend our investigation to other substrates and establish its wider applicability.

Allylic and benzylic PMB ethers reacted rapidly as compared to the aliphatic PMB ethers, which required long reaction times to achieve yields comparable with those of their allylic and benzylic counterparts. This



1 4

Scheme 3.



1 5

Scheme 4.

method is also highly effective in transforming PMB ethers to bromides in the presence of other hydroxyl protecting groups such as OBn, OAc, OMe, OBz and diacetonide (entries m, n, o, p and s).

It is important that the substrates with stereogenic centers (entries e and s), afforded bromides with complete retention of the original configuration. No *cis–trans* isomerization was observed and hence substrates with *E* or *Z* olefins retained their respective geometries in the isolated products (entries a, b, c, e, i and t).

It was interesting to observe that a free hydroxyl in the presence of PMB ether was transformed to the bromide leaving the PMB ether unaffected when subjected to 1 equiv. of the reagent (1:2, CBr_4:TPP), but when 2 equiv. (2:4, CBr_4:TPP) was employed, dibromides were the resultant products (entries k, l).

It is also important to note that the rates of transformation of THP, silyl and PMB ethers were found to be the same. Hence, when substrates bearing these functionalities (entries c, q and r) were treated with 1 equiv. of the reagent (1:2, CBr_4:TPP), the product isolated was the dibromide in 40–45% yield, with the remainder being the recovered starting material; when treated with 2 equiv. of the reagent, the dibromide was obtained with yields in the range of 80–88%.

In the case of benzylic substrates, the TLC analysis showed the presence of two products, i.e. the corresponding alkyl bromide and PMB bromide and the products were isolated by preparative thin layer chromatography (TLC).

This method is highly chemoselective for the transformation of PMB ethers to their respective bromides leaving other functional groups such as olefins and carbonyl groups intact. Conditions were standardized[5] and the products were fully characterized.[6] It was found that the best results were obtained by the use of 1 equiv. of the reagent (1:2, CBr_4:TPP) at 0°C for 30 minutes to 3 hours.

3. Mechanism

The mechanism proposed is the same as that proposed for transformations of THP and silyl ethers to bromides.[2c] Two moles of TPP and one mole of CBr_4 react to give two species, **I** and **II** (Scheme 5).[2m] Species **I** transforms carbonyl groups to dibromo olefins whereas species **II**, i.e. TPP and Br_2 is the main brominating agent.

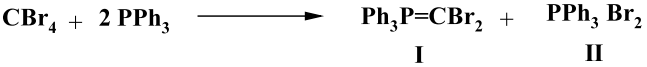
Accordingly the complex of TPP and Br_2 formed in situ, reacts with PMB ethers to give the alkyl bromides, triphenyl phosphine oxide and PMB bromide (Scheme 6).

But we did not observe any PMB bromide (except in the case of aromatic substrates) on TLC analysis. A literature survey revealed that benzyl bromide reacts with TPP–dibromomethylene **I**, in anhydrous CH_2Cl_2 to give (1,1-dibromo-2-phenyl)-ethyl-triphenyl-phosphonium bromide as a salt.[2m]

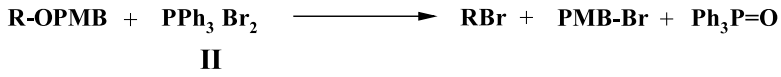
Based on this, we assumed that PMB bromide, formed in situ, also reacts with **I**, forming the salt **III** (Scheme 7), and hence PMB bromide was not observed on TLC analysis. Accordingly, we isolated the salt **III** as a benzene insoluble component from the reaction mixture and characterized it by ^1H NMR and melting point analysis.[7]

To further confirm the mechanism, the same set of reactions was carried out with TPP and Br_2. The TLC analysis of the reaction mixture indicated a complex mixture and the products formed were inseparable. The proton NMR of the crude product exhibited a mixture of respective alkyl bromide and PMB bromide, hence confirming the proposed mechanism.

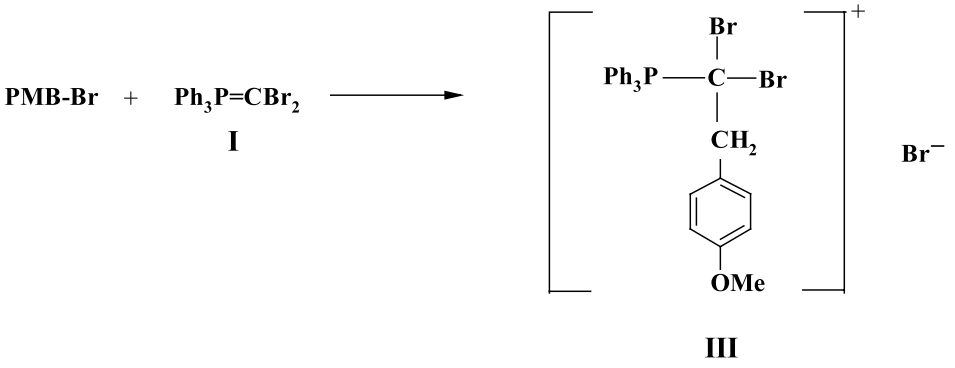
In summary, this paper describes a simple and highly efficient method for the conversion of PMB ethers to bromides by the CBr_4–TPP reagent system. Furthermore, it is established that the CBr_4–TPP reagent system is superior to TPP and Br_2 as in the former case the alkyl bromide is the only observed product, as PMB bromide formed in situ reacts with **I** forming the salt **III**, thereby making isolation a simple procedure. Moreover, it is hazardous to use bromine, hence the use of the CBr_4–TPP reagent system is a more eco-friendly



Scheme 5.



Scheme 6.



Scheme 7.

procedure. Thus the high level of chemoselectivity combined with simple operation, and high yields of products should facilitate the wider use of this process in multi-step syntheses.

Acknowledgements

R.K.M. thanks CSIR, New Delhi for financial assistance in the form of a senior research fellowship.

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5. **General procedure for the transformation**: To a cooled solution of CBr_4 (1 mmol) in anhydrous CH_2Cl_2 at 0°C was added dropwise a solution of TPP (2 mmol) in anhydrous CH_2Cl_2 over a period of 15–20 min. The resultant mixture was stirred at 0°C for a further 20 min, followed by addition of a solution PMB ether (1 mmol) in anhydrous CH_2Cl_2 to the orange colored solution. The reaction was monitored by TLC. After all the PMB ether was consumed, the mixture was concentrated to a small volume. Petroleum ether was added to the residue, the precipitate formed was filtered off. The precipitate was washed several times with petroleum ether. The filtrate was concentrated under reduced pressure and the crude product was purified on silica gel column chromatography using hexane and ethyl acetate as the eluent (98:2 to 97:3, hexane:ethyl acetate).
6. All new compounds were fully characterized by ^{1}H NMR, MS, FAB MS and IR. Spectroscopic data for selected compounds. **4**: IR (neat), 820, 1210, 1640 cm^{-1}; ^{1}H NMR (200 MHz) 1.3 (10H, m), 1.4 (4H, m), 2.05 (4H, m), 3.95 (2H, d, J=12.6 Hz), 5.7 (2H, m), 6.39 (1H, t, J=9.6 Hz). FAB MS m/z (rel. int%) 431 (18), 433 (55.8), 435 (54), 437 (18). **5**: IR (neat), 1210, 1730 cm^{-1}; ^{1}H NMR (200 MHz) 1.3 (12H, m), 1.62 (2H, m), 2.09 (2H, m), 2.4 (2H, m), 3.95 (2H, d, J=13Hz), 5.7 (2H, m), 9.79 (1H, s). MS (EI) m/z (rel. int%) 275 (18.5), 277 (18.4).
7. **Isolation and characterization of III:** Removal of solvent from the reaction mixture gave benzene insoluble **III** and benzene soluble bromoalkane and triphenylphosphine oxide. Melting point: 192–194°C. ^{1}H NMR (200 MHz): 3.01 (s, 2H), 3.8 (s, 3H), 6.92 (d, J=7.5 Hz, 2H), 7.17 (d, J=7.5 Hz, 2H), 7.6–7.8 (m, 15H). Cf. Ref. 2m.