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Counterattack Mode Differential Acetylative Deprotection of Phenylmethyl Ethers: Applications to Solid Phase Organic Reactions

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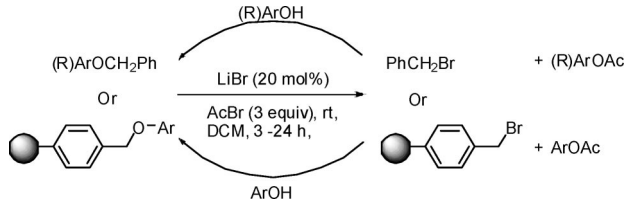
Received July 29, 2008



A counterattack protocol for differential acetylative cleavage of phenylmethyl ether has been developed. The phenylmethyl moiety is liberated as benzyl bromide that is isolated and reused providing advantages in terms of waste minimization/utilization and atom economy. The applicability of this methodology has been extended for solid phase organic reactions with the feasibility of reuse of the solid support.

Protecting groups (PGs), albeit often under-appreciated, constitute key components in drug synthesis amounting to >20% of all chemical transformations and about two key steps per drug candidate.[1] The overall merit of a synthetic process is highly influenced by the interplay of physicochemical properties, ease of introduction, cost-effectiveness, and selective manipulation of PGs. The protection and deprotection of the hydroxyl group are encountered with 30% and 14% frequency, respectively, in the manufacturing process of drugs.[1] In this context, the phenylmethyl ether formation is the most common practice for protecting hydroxyl groups.[2] We describe herein a convenient and high-yield protocol for acetylative cleavage of phenylmethyl ethers with AcBr (3 equiv)−LiBr (20 mol %) with high chemo- and regioselectivities.[3]

Since the utility of a PG is associated with its ease of removal without affecting other protecting/functional groups, the scope of the de-*O*-benzylation was evaluated with various substituted phenylmethyl ethers (Table 1).

Substrates bearing electron donating group such as alkyl or alkoxy reacted readily with excellent yields (entries 2, 12−20; Table 1). The presence of an electron withdrawing group gave poor to moderate yields (entries 3−6 and 8−10; Table 1) and required longer time. However, in all the cases the starting materials could be recovered and reused/recycled increasing the overall yield of the products. The presence of a halogen atom, OR, and COMe adjacent to the benzyloxy group assisted the de-*O*-benzylation (compare entry 1 with 17; 5 with 18; 6 with 7; 10 with 11; Table 1). Excellent regioselectivity was obtained with substrates containing both benzyl and nonbenzyl ether moieties (entries 16−20, 23, 25, 28, 30, and 31) with exclusive de-*O*-benzylation. In the case of benzyl cinnamyl ether (entry 27), selective deprotection at the cinnamyl ether was observed. For substrates having primary and secondary benzylic ether moieties (entry 26), de-*O*-benzylation occurred at the primary benzyl ether. Methyl ether, methyl ester, and benzyl ester groups remained unaffected (entries 9, 16−20, 23, and 32; Table 1).

Good conversion took place with AcBr-LiCl, albeit lesser than that of AcBr−LiBr, but the replacement of LiBr by LiI and LiF was ineffective. Halides (fluoride/chloride/bromide/iodide) of other metals, e.g., Na, K, Cs, Rb, Ca, and Mg, were either ineffective or gave poor conversion. The use of AcCl, AcOH, and Ac_2O in combination with LiBr was also ineffective. No significant ether cleavage was observed in using AcBr or LiBr (stoichiometric amount) alone at rt or under reflux for 24 h. Replacement of DCM by other solvents such as DCE, MeCN, DMF, and NMP did not offer any significant deprotection at rt or under reflux. The use of ethereal solvents such as THF and dioxane was also limited due to their reaction with the reagent system. The protocol was effective at low temperature (ca. −40 °C) with marginal decrease in conversion suggesting the feasibility of application for highly reactive substrates under mild conditions.

The course of the reaction is depicted in Scheme 1 and accounts for the observed reactivity and selectivity. Electrophilic activation of AcBr by coordination with LiBr[4] followed by nucleophilic attack by the oxygen atom of the ether and counterattack by the liberated Br^- at the benzylic carbon through the cyclic structure **I** leads to the acetylated product and benzyl bromide.

Since, the efficiency of the reaction should depend upon the nucleophilic property of the oxygen atom of the benzyl ether, (i) de-*O*-benzylation of benzyl ethers of alcohols took place at faster rates than that of the benzyl ethers of phenols (compare entries 1−23 with 24−31; Table 1), and (ii) the presence of an electron withdrawing group makes the deprotection sluggish (entries 3−6 and 8−10; Table 1). The unusual reactivity of substrates having halogen atom, OR, and COMe groups adjacent

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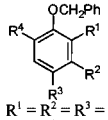
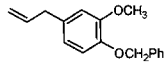
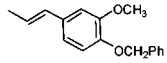
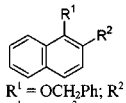
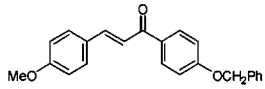
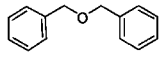
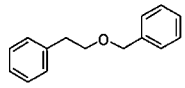
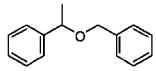
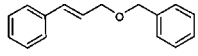
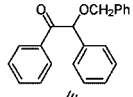
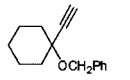
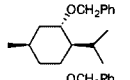
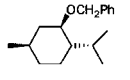
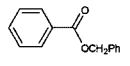
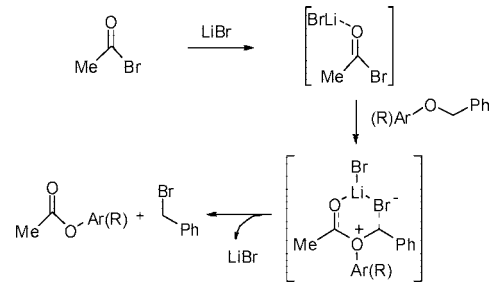
10.1021/jo801659g CCC: $40.75
Published on Web 12/31/2008

TABLE 1. AcBr−LiBr-Mediated Acetylative Cleavage of Arylmethyl Ethers[a]

entry	substrate	time (h)	yield (%)[b,c]
			
1	$R^1 = R^2 = R^3 = R^4 = H$	24	92[d]
2	$R^1 = R^2 = R^4 = H$; $R^3 = OCH_2Ph$	12	83[e,f]
3	$R^1 = R^2 = R^4 = H$; $R^3 = NO_2$	24	34(60)
4	$R^1 = R^3 = R^4 = H$; $R^2 = NO_2$	24	40(65)
5	$R^1 = R^2 = R^4 = H$; $R^3 = Br$	24	40(67)
6	$R^1 = R^2 = R^4 = H$; $R^3 = Cl$	24	38(62)
7	$R^1 = Cl$; $R^2 = R^3 = R^4 = H$	24	90
8	$R^1 = R^2 = R^4 = H$; $R^3 = CN$	24	38(65)
9	$R^1 = R^2 = R^4 = H$; $R^3 = CO_2Me$	24	40(68)
10	$R^1 = R^2 = R^4 = H$; $R^3 = COMe$	18	63(80)
11	$R^1 = COMe$; $R^2 = R^3 = R^4 = H$	12	78
12	$R^1 = R^2 = R^4 = H$; $R^3 = Me$	12	86
13	$R^1 = R^3 = R^4 = H$; $R^2 = Me$	12	80
14	$R^1 = R^3 = R^4 = Me$; $R^2 = H$	12	96
15	$R^1 = R^2 = R^4 = H$; $R^3 = {}^iPr$	12	83
16	$R^1 = R^2 = R^4 = H$; $R^3 = OMe$	12	97
17	$R^1 = OMe$; $R^2 = R^3 = R^4 = H$	6	98
18	$R^1 = Br$; $R^2 = R^4 = H$; $R^3 = OMe$	24	83
19		12	80
20		12	75
21	 $R^1 = OCH_2Ph$; $R^2 = H$	24	70
22	$R^1 = H$; $R^2 = OCH_2Ph$	24	90
23		24	60(77)
24		6	96
25		6	90[g]
26		4.5	90[h]
27		6	98[i]
28		3	80[j]
29		3	44(70)
30		3	70[k]
31		3	80[l]
32		24	nil[m]

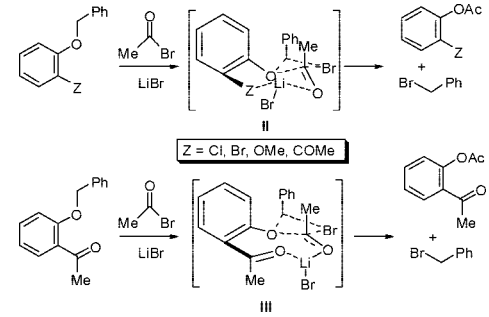
[a] The substrate (1 mmol), AcBr (3 mmol, 3 equiv), and LiBr (20 mol%) in dry DCM were stirred magnetically at rt (30−35 °C) under argon. [b] Yield of *O*-acetylated derivative of the corresponding phenol/alcohol. [c] The figure in parentheses represents the yield on the basis of recycling of the recovered starting material. [d] Phenol was isolated as the product. [e] Yield of 4-benzyloxyphenyl acetate. [f] The corresponding phenol was obtained in 6% yield. [g] Yield of 2-phenethyl acetate. [h] Yield of 1-phenethyl acetate. [i] Yield of benzyl acetate. [j] Yield of *O*-acetylbenzoin. [k] Yield of (+)-(1*S*,2*R*,5*R*)-isomenthyl acetate. [l] Yield of (−)-(1*R*,2*S*,5*R*)-menthyl acetate. [m] The starting material remained unchanged and was recovered.

SCHEME 1. The Role of AcBr−LiBr in Acetylative Deprotection of Phenylmethyl Ethers



I

SCHEME 2. The Chelation Effect of a Neighboring Group

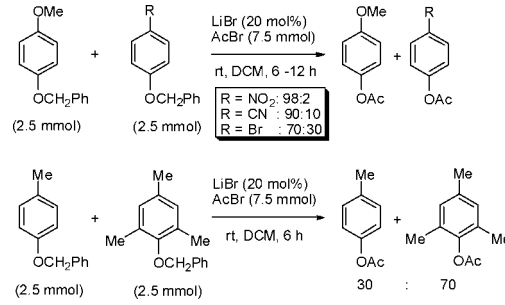


II

Z = Cl, Br, OMe, COMe

III

SCHEME 3. Differential Deprotection during Intermolecular Competition between Phenylmethyl Ethers with Varying Electronic Environment

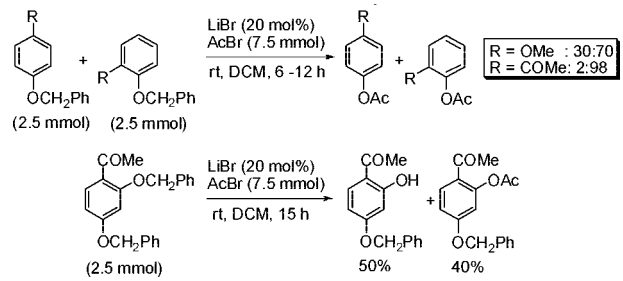


to the benzyl ether moiety (entries 7, 11, and 17−20) is due to the chelation effect (Scheme 2) of these groups in providing assistance of nucleophilic attack by the oxygen atom of the benzyl ether on the AcBr (complexed with LiBr) and nestling the incipiently formed Br^- in appropriate orientation/position for nucleophilic attack at the benzylic carbon of the ether through the cyclic structure **II/III**.

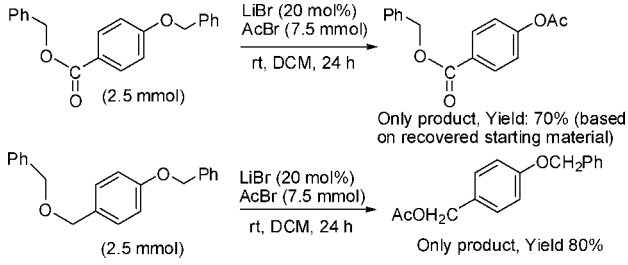
The influence of the electronic environment in the substrates on the reaction time and yield of de-*O*-benzylations encouraged us to demonstrate the potentiality of this protocol for selective deprotection of benzyl ethers during intermolecular competitions. Treatment of equimolar mixtures of (i) 4-methoxyphenylbenzyl ether and 4-nitrophenylbenzyl ether, (ii) 4-methoxyphenylbenzyl ether and 4-cyanophenyl benzyl ether, and (iii) 4-methoxyphenylbenzyl ether and 4-bromophenylbenzyl ether for 6, 6, and 12 h afforded selectivities (GCMS) of 98:2, 90:10, and 70:30, respectively, in favor of acetylative de-*O*-benzylation of 4-methoxyphenylbenzyl ether. The reaction of 4-methylphenylbenzyl ether and 2,4,6-trimethylphenyl benzyl ether resulted in 30:70 selectivity (Scheme 3).

The chelation effect of an adjacent group in differenting the rate of de-*O*-benzylation was utilized for selective deprotection

SCHEME 4. Chelation Effect of the Neighboring Group for Differential Deprotection of Phenylmethyl Ethers during Intermolecular and Intramolecular Competition Studies



SCHEME 5. Differential Deprotection of Phenylmethyl Ether during Intramolecular Competition Studies

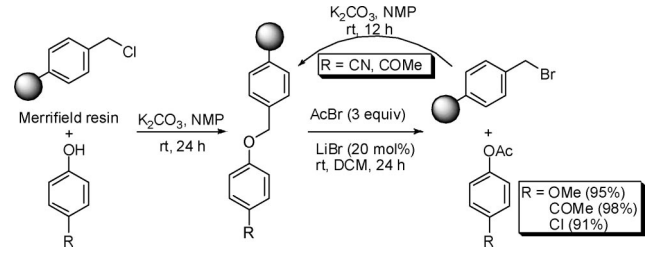


during intermolecular and intramolecular competiton studies (Scheme 4). Reactions of equimolar mixtures of (i) 4-methoxyphenylbenzyl ether and 2-methoxyphenylbenzyl ether and (ii) 4-acetylphenylbenzyl ether and 2-acetylphenylbenzyl ether afforded selectivities (GCMS) of 30:70 and 2:98, after 6 and 12 h, respectively. The reaction of 2,4-dibenzyloxy acetophenone exhibited exclusive selectivity in favor of de-*O*-benzylation of the phenylmethyl ether adjacent to the COMe group affording 2-hydroxy-4-benzyloxy acetophenone (**I**) and 2-acetoxy-4-benzyloxy acetophenone (**II**) in 50% and 40% yields, respectively. The acetylated product **II** was formed as the only product in 40% yield when the reaction was carried out for 6 h and the unreacted starting material was recovered. A 60% yield of **I** was obtained after 12 h along with 25% of **II** and 5% of the diacetyl derivative of the di-de-*O*-benzylated compound.

Excellent selectivity was achieved in intramolecular competition between (i) benzyl ether and benzyl ester and (ii) benzyl ethers of phenol and alcohol (Scheme 5). The reaction of benzyl 4-benzyloxybenzoate underwent cleavage of the benzyl ether group exclusively in 40% yield. The unreacted starting material was recovered and reused/recycled to increase the overall yield to 70%. The use of 6 equiv of AcBr afforded 65% yield. In the case of 4-benzyloxyphenylmethyl phenylmethyl ether, deprotection of the alcoholic benzyl ether group took place exclusively affording the corresponding acetylated product in excellent yield.

Differential cleavage of arylmethyl ethers has been reported with use of $CrCl_2$ (3 equiv)/LiI (4 equiv) in moisture containing EtOAc.[5] The recent reports on the use of protic acids for the deprotection of aromatic ethers[3a,b] often leading to undesired ring alkylation and requiring a large excess of thioanisole to suppress the side reaction, which are not applicable to electron-rich phenolic ethers that generate complex mixtures of Friedel−Crafts byproduct, are suitable only for phenolic ethers with an *ortho* π-electron-withdrawing group and do not work with alkyl benzyl ethers. The reported acetylative de-*O*-benzylation required stoichiometric amounts of $F_3B\cdot OEt_2$ and NaI in Ac_2O as solvent.[6] The hydrogenolysis protocols[3c−e] lacking chemoselectivity and a NO_2 group or an olefinic unsaturation undergo reduction. Under hydrogenolysis conditions, the benzyl moiety is lost as the corresponding hydrocarbon (e.g., toluene) and lacks atom efficiency.[7] Under the present methodology, the phenylmethyl moiety is liberated as benzyl bromide that was recovered and reused for phenylmethyl ether formation. The increasing influence of green chemistry on chemistry based research organization[8] and the tight legislation[9] on chemical processes to prevent waste, avoid use of toxic substances,[10] etc. press the need for sustainable development. The use of cheap, easy to handle, and less toxic LiBr as catalyst and high yield, devoid of side reaction, are the distinct advantages offered by this newly developed protocol. The reusability of the benzyl bromide adds another dimension to this protocol and provides an approach toward sustainable development in terms of waste minimization/utilization and atom economy.[7]

SCHEME 6. Cleavage of Phenylmethyl Ether Supported on Merrifield Resin and Recycling of the Solid Support



The scope of this de-*O*-benzylation protocol was extended to the solid phase organic reaction (SPOR) (Scheme 6). The progress of the reaction and loading on the solid phase was monitored/determined by FTIR.[11] In model studies 4-hydroxy acetophenone and 4-methoxy phenol loaded on Merrifield resin were subjected to de-*O*-benzylation to regenerate the corresponding phenols in 98% and 95% yields, respectively. The recovered resin was the corresponding bromide form (FTIR, DSC) and was reused for loading of 4-hydroxyacetophenone and 4-cyanophenol. The loading of the phenolic substrates on the recovered solid support required shorter times and highlighted the advantage of the reuse of the recovered resin.

The applicability for SPOR was further demonstrated by generating a six-component solid phase library by loading six different phenols on Merrifield resin and treatment of the solid phase library with AcBr−LiBr to liberate the parent phenols and the resin as its bromide form (Scheme 7).

In conclusion, a counterattack mode differential acetylative deprotection of phenylmethyl ethers has been developed. The benzyl ether moiety that is liberated as benzyl bromide is reused and offers an advantage through waste minimization/utilization.[9]

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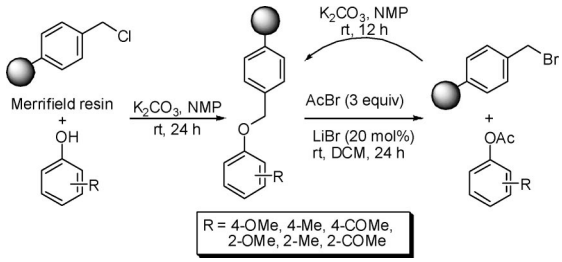
SCHEME 7. Six-Component Solid Phase Library Synthesis and Cleavage of Phenols from Solid Support



The applicability of this methodology has been extended for solid phase organic reactions with the feasibility of reuse of the solid support.

Experimental Section

Typical Experimental Procedure for the LiBr−AcBr-Catalyzed Cleavage of Aryl Benzyl Ethers: 2-Acetylphenyl Acetate (Entry 11, Table 1). To a magnetically stirred solution of 2-benzyloxyacetophenone (0.56 g, 2.5 mmol) and AcBr (0.93 g, 7.5 mmol, 3 equiv) in DCM (5 mL) was added LiBr (43 mg, 20 mol %). The reaction mixture was stirred at 30−35 °C for 12 h. After completion of the reaction (TLC), the reaction mixture was diluted with water (1 mL) and EtOAc (15 mL). The organic layer was separated and washed with water (10 mL) and brine solution (10 mL), dried (anh Na_2SO_4), and concentrated under rotary vacuum evaporation. The residue was subjected to column chromatography purification (60−120 mesh silica gel 20 g, 5% EtOAc in hexane) to afford 2-acetylphenyl acetate as an oil (0.35 g, 78%), identical (IR, NMR, and EIMS) with an authentic sample.[12]

Typical Experimental Procedure for Chemoselective *O*-Debenzylation of Benzyl Ethers during Intermolecular Competition Studies (Scheme 3): 1-(Benzyloxy)-4-methoxybenzene vs 4-Benzyloxynitrobenzene. To a magnetically stirred solution of 1-(benzyloxy)-4-methoxybenzene (0.53 g, 2.5 mmol), 4-benzyloxynitrobenzene (0.57 g, 2.5 mmol), and AcBr (0.93 g, 7.5 mmol, 3 equiv) was added LiBr (43 mg, 20 mol %). The reaction mixture was stirred at 30−35 °C for 12 h. The reaction mixture was diluted with water (1 mL) and EtOAc (15 mL). The organic layer was separated and washed with water (10 mL) and brine solution (10 mL), dried (anh Na_2SO_4), and concentrated under rotary vacuum evaporation. The residue was subjected to column chromatography purification (60−120 mesh silica gel 20 g, 5% EtOAc in hexane) to afford 4-methoxyphenyl acetate and 4-nitrophenyl acetate in 98% and 2% yields, respectively.

Typical Experimental Procedure for Solid Phase Organic Reaction: Representative Procedure for Cleavage of Merrifield Resin-Bound Ether. To the suspension of Merrifield resin bound 4-hydroxy acetophenone [(0.375 mmol, 150 mg, preswelled in DCM (2 mL) for 0.5 h)] was added the mixture of LiBr (20 mg, 60 mol %) and AcBr (3.00 mmol, 0.234 mL, 3 equiv) in DCM (4 mL) under argon and the resulting mixture was stirred magnetically for 24 h at room temperature. The resin was collected by filtration and the filtrate was washed with 5% aq $NaHCO_3$ (4 mL) and acidified with 5% HCl solution. The organic layer was dried (anh Na_2SO_4) and concentrated under rotary vacuum evaporation to afford the product (IR, ^{1}H NMR, and MS). The solid support was washed with NMP (3 × 5 mL), water (3 × 5 mL), MeOH (3 × 5 mL), and acetone (3 × 5 mL), respectively. The recovered resin was dried under vacuum for 0.5 h and was found to be the bromo derivative of the Merrifield resin exhibiting characteristic absorption at 1245−1250 cm^{-1} in the FTIR (the original Merrifield resin has characteristic absorption at 1263 cm^{-1} of the CH_2Cl moiety).[11a] The resin was reused for further reaction.

Reuse of the Bromo-Derived Merrifield Resin Recovered after Deprotection. The bromo-derived Merrifield solid support (0.575 mmol, 250 mg) was swelled for 4 h in dry NMP (2 mL). Simultaneously, in a separate reaction flask 4-cyanophenol (0.21 g, 3 equiv) and K_2CO_3 (3.6 equiv) were stirred in NMP under argon atmosphere for 4 h. The potassium salt was transferred to the swelled Merrifield support and the mixture was stirred for 24 h. The mixture was filtered through a sintered glass funnel. The solid support was washed with NMP (3 × 5 mL), water (3 × 5 mL), MeOH (3 × 5 mL), and acetone (3 × 5 mL), respectively. The resin was dried over vacuum for 30 min. The loading was determined by FTIR and Synthesis Monitoring System (SMS). In the FTIR, complete disappearance of the absorption at 1245−50 cm^{-1} and appearance of the nitrile signal at 2223 cm^{-1} indicated completion of the reaction.

Supporting Information Available: Spectral data of all compounds and scanned spectra of a few representative known and all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801659G

(12) Chakraborti, A. K.; Gulhane, R.; Shivani, *Synthesis* **2003**, 111.