SHORT PAPER

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A facile aromatic C-benzylation with phosphorodithioate esters under Friedel-Crafts conditions

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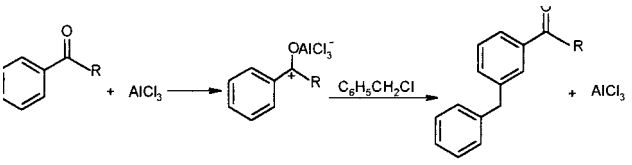
Benzyl or substituted benzyl phosphorothionothiolates (**1a–f)** on treatment with anhydrous aluminium chloride in benzene at reflux temperature undergo cleavage of the C-S bond with formation of aromatic ring benzylated products (**2a–f**) in very good yield.

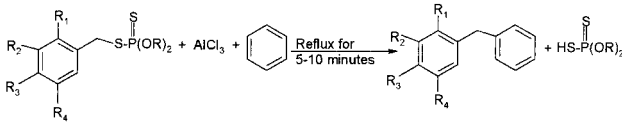
The development of efficient and selective methods for the construction of C–C bond is a challenging and exciting endeavour in organic synthesis.[1,2] Aromatic ring benzylation is an important C–C bond formation reaction for synthesis of many biologically important molecules.[3,4] Although there are several *O*-benzylation[5] and *N*-benzylation[6] methods available in the literature, reports of aromatic *C*-benzylations are very few. On the other hand most of the reported[7–9] methods give very poor yields and are time consuming. The Friedel–Crafts reaction[10,11] is the most convenient and extensively used method for such a purpose. However, sensitivity of most of the Lewis acid catalysts towards certain specific groups present in some substrates is still a major drawback in the Friedel–Crafts reaction. As, for example, benzylation of aromatic ketones or aldehydes with benzyl halide in presence of anhydrous aluminium chloride is very poor reaction owing to the complex formation between the carbonyl oxygen and aluminium chloride (Scheme 1).[10b] With a Lewis acid, an electron deficiency is generated on the carbonyl carbon by coordination of the oxygen of the carbonyl group with the open sextet of the Lewis acid. As a result the desired reaction product is accompanied by several polymeric and other side materials. Use of intercalated montmorillonite composites[12] as a substitute for Lewis acid is currently receiving considerable attention for overcoming such problems. Spectacular progress in this direction has yet to be achieved.



R=H,alkyl or aryl

Scheme 1

Although phosphorus carbon bond formation under Friedel–Crafts conditions was reported earlier[13] formation of a C–C bond by aralkylation using organophosphorus reagents under similar conditions has not been reported so far. As a part of our programme on the syntheses of biologically active organophosphorus compounds we were interested in the possibility of using such compounds as potential substrates for Friedel–Crafts reactions. We observed that when the benzyl ester of *O,O*-dimethyl phosphorodithioic acid is refluxed with anhydrous aluminium chloride in dry benzene, formation of a benzyl derivative by electrophilic substitution on the aromatic ring takes place within 5–10 minutes giving 90–95% yield of the products (Scheme 2).



1 **2**

R=Me

a; R_1=R_2=R_3=R_4=H

b; R_1=OH, R_2=R_3=R_4=H

c; R_1=R_2=R_4=H,R_3=OH

d; R_1=OH,R_2=R_4=H,R_3=Cl

e; R_1=OH,R_2=R_3=H,R_4=COMe

f; R_1=OH,R_2=COMe,R_3=H,R_4=Me

Scheme 2

The presence of a carbonyl group or other substituents in the aromatic ring does not interfere in the reaction at all. In this reaction solvent benzene takes part as one of the substrates. The formation of the products (**2a–f**) can be unequivocally discerned in the following way. The activation energy for the formation of the coordination complex of aluminium chloride and the *O,O*- dimethyl phosphorodithioate moiety is probably sufficiently low compared to the formation of a similar complex with a carbonyl moiety. This is because the easy polarizability of the P=S bond compared to the C=O bond facilitates the coordination of sulfur atom of the dithioate moiety with the open sextet of the Lewis acid . This favours easy cleavage of the weak C–S bond of the benzyl ester. *O,O*-Dimethyl phosphorodithioic acid liberated after formation of the C-benzylated product was isolated as its methyl ester by reacting with methyl iodide.

The products **2a–d** are commercially used as very good germicides.[3,4] The easy reaction conditions and high yields of these products make the above methodology an attractive alternative to their formation.

Experimental

Melting points reported are uncorrected. PMR spectra were recorded on Varian T-60 NMR spectrometer, IR spectra were recorded on a

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Benzene is highly toxic and is a **carcinogen.** It causes irritation on mucous membrane and a harmful amount may be absorbed through the skin**.** It is also highly inflammable and the vapour forms explosive mixtures with air. The reaction should therefore be carried out with stringent containment measures in a fume cupboard with proper use of rubber hand gloves and mask.

Table 1 Physical characteristics and the yields of the products **2a-f**

Substrate	Product*	Melting point/°C found	Literature	Yield %
1a	**2a**	22–24	24[4a]	95
1b	**2b**	53	52[4c]	89
1c	**2c**	80	82[4c]	91
1d	**2d**	48	48.5[4b]	91
1e	**2e**	70	—	90
1f	**2f**	84	—	93

Perkin Elmer 237B spectrometer and mass spectra on an AEI MS Finnigan Mat 50 spectrometer. *O,O*-Dimethyl phosphorodithioic acid was prepared by the method reported earlier.[14]

Preparation of O,O-dimethylphosphorothiono-3-acetyl-2-hydroxy-5-methyl benzyl thiolate **(1f)** *(R=CH$_3$):* A mixture of 3-chloromethyl-2-hydroxy-5-methyl acetophenone[15] (1g, 5.8 mmol), anhydrous potassium carbonate (1g,7.2 mmol) and 40% *O,O*-dimethyl phosphorodithioic acid in benzene (20 ml) was refluxed on an oil bath for 2–3 hours under vigorous stirring. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled, filtered and the filtrate was washed with water (3×50 ml) to remove the inorganic impurities. The filtrate was then dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude ester. Yellowish crystals of **1f** were obtained by purifying the crude ester on a silica gel column using 50% petroleum ether in benzene. Alternatively 20% dichloromethane in petroleum ether can be used as an eluent to avoid benzene. Yield 1.28 g(80%), m.p. 99.5°C(Lit[10] 100°C), ν_{max} cm^{-1}(KBr) 3300,2935,1637,1190,650; δ_H(CCl_4) 2.11(s,3H,Ar-CH_3),2.43(s,3H,CO CH_3),3.53 (d,$^4J_{P\text{-}O\text{-}C\text{-}H}$= 15Hz,6H,2×$CH_3$),3.86(d,$^4J_{P\text{-}S\text{-}C\text{-}H}$=15Hz,2H,Ar–$CH_2$), 7.35(d,*J*=2Hz,1H,Ar–6–H),7.31(d, *J*=2Hz,1H,Ar–4–H),12.06(bs,1H, Ar-OH);*m/z*320(M^+);(Found,C,44.45;H,5.63;$C_{12}H_{17}O_4PS_2$ requires C,45.00; H,5.31).

Preparation of 3-benzyl-2-hydroxy-5-methyl acetophenone **(2f)***: O,O*-Dimethyl phosphorothiono 3-acetyl-2-hydroxy-5-methyl benzyl thiolate (**1f**) (0.462g, 1.4 mmol) was taken in dry benzene[#] (50 ml) and placed the solution in a round bottomed flask fitted with a reflux condenser. Then anhydrous aluminium chloride (0.507 g,3.8 mmole) was added to the reaction flask. The whole mixture was then refluxed for 5–10 minutes. The reaction mixture was cooled to room temperature, poured on to crushed ice (20 g) and stirred vigorously. After separation of the organic layer it was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the product was crystallized from petroleum ether to get 3- benzyl-2-hydroxy-5-methylacetophenone (**2f**).Yield 0.34g (93%), m.p. 84°C, ν_{max}cm^{-1}(KBr) 3200,2900, 1648,1425, 1250,750; δ_H(CCl_4)1.73(s,3H, Ar–CH_3), 2.05 (s,3H,$COCH_3$) 3.46(s, 2H, Ar–CH_2), 6.70-7.20(m, 7H, ArH), 11.8(bs,1H, Ar–OH); *m/z* 240 M^+; (Found C, 79.78; H, 6.60, $C_{16}H_{16}O_2$ requires C,80.00; H,6.66).

Methylation of O,O-dimethyl dithiophosphoric acid: The aqueous layer obtained after separation of **2f** was treated with sodium hydroxide solution (10%) and washed it with ethyl acetate to remove the organic impurities. The alkaline layer was then taken with dichloromethane (50 ml) and stirred with methyl iodide(5 ml) at room temperature for about half an hour in presence of tetraethyl ammonium iodide (TEAI, 0.1%) phase transfer catalyst. The methyl ester of *O,O*-dimethyl phosphorodithioic acid thus formed was then separated and washed with cold water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to get a syrupy oil. It was then characterized from its NMR, IR and mass spectral data which are in accord with the reported values.[16–18]

*3-Benzyl-4-hydroxy acetophenone***(2e):** Prepared as above. Yield 0.23 g (90%), m.p. 70°C, ν_{max}/cm^{-1}(KBr) 3325,1685, 1500, 1280, 860,780; δ_H(CCl_4) 2.43 (s,3H,$COCH_3$), 3.13(s,2H,Ar-CH_2),6.80 (d, *J*=8Hz, 1H, Ar-5-H),7.18–7.60(m,6H,ArH),11.5(s,1H,Ar-OH); *m/z* 226 M^+. (Found C, 79.12; H,6.32 $C_{15}H_{14}O_2$ requires C, 79.64; H, 6.19).

Similarly the other derivatives **2a-d** were prepared and characterized from their IR, NMR, mass spectra and elemental analyses data and found in accord with the reported values in the literature.[19–22] The physical characteristics and the yields are given in Table 1.

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