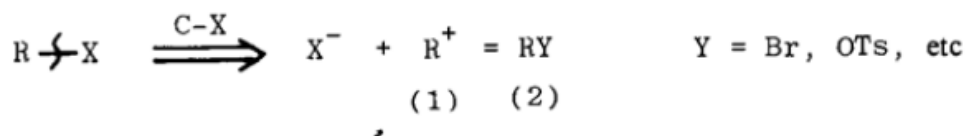


## Lecture # 5

# One-Group C-X Disconnections

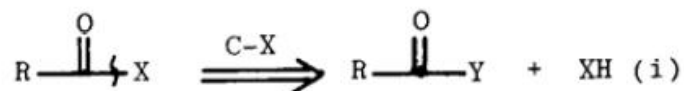
We started with aromatic compounds because the position of disconnection needed no decision. We continue with ethers, amides, and sulphides because the position of disconnection is again easily decided: we disconnect a bond joining carbon to the heteroatom (X). This approach is fundamental to synthetic design and is a 'one-group disconnection' since we need to recognise only one functional group to know that we can make the disconnection. The label 'C-X' or 'C-N' etc. can be used.

The corresponding reactions are mostly ionic and involve nucleophilic heteroatoms as in alcohols (ROH), amines (RNH<sub>2</sub>), or thiols (RSH). The disconnection will therefore give a cationic carbon synthon (1). The reagent for (1) will usually have a good leaving group attached to R (2). In other words, the reaction is a substitution of some kind and the reagents will be alkyl halides, acid chlorides, and the like and the best reagents will be those which undergo substitution most readily.



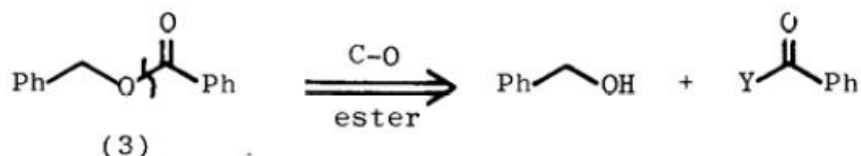
### Carbonyl Derivatives RCO.X

Acid derivatives are easy to disconnect since we almost always choose the bond between the carbonyl group and the heteroatom for our first disconnection (i).



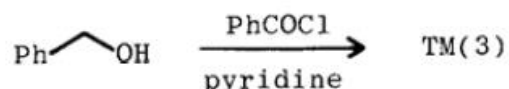
The ester (3), used both as an insect repellent,<sup>31</sup> and as a solvent in perfumery,<sup>32</sup> invites this disconnection.

### Analysis



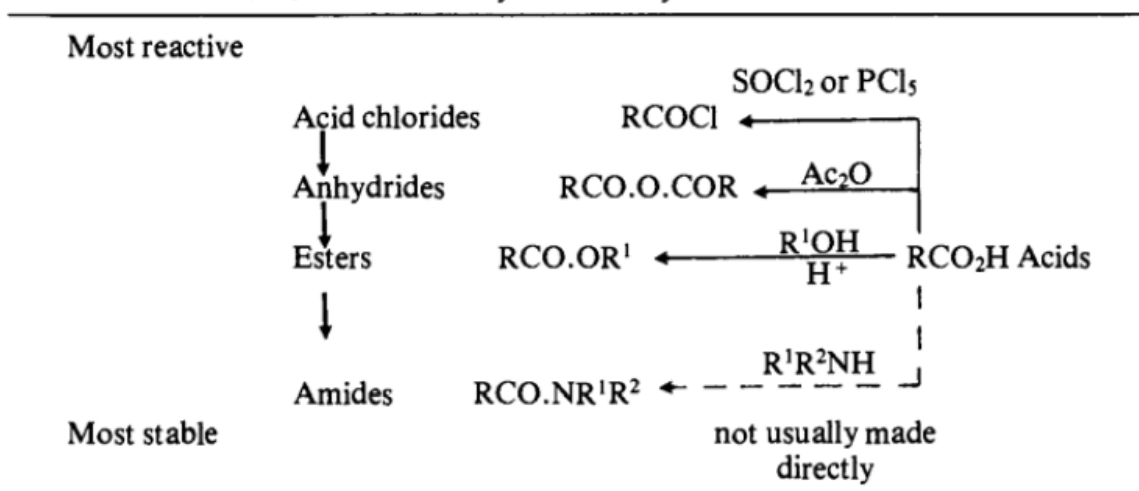
The synthesis can be carried out in a number of ways: perhaps the acid chloride route (Y=Cl) is the easiest, with pyridine as catalyst and solvent.

### Synthesis



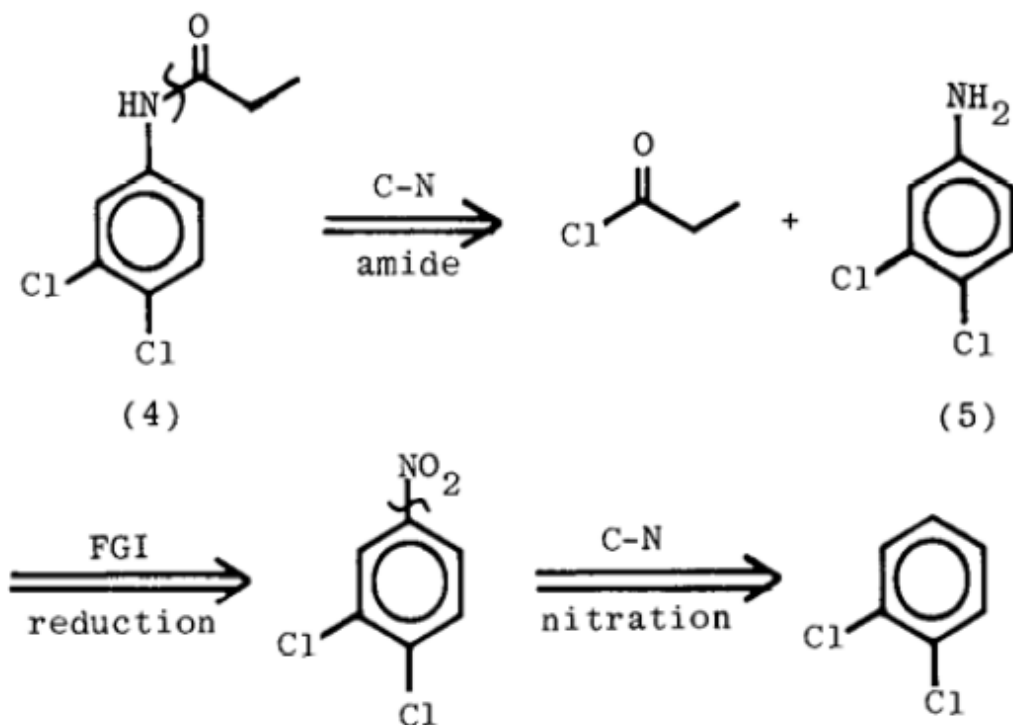
Acid chlorides are often used in these syntheses because they are the most reactive of all acid derivatives and because they can be made from the acids themselves and  $\text{PCl}_5$  or  $\text{SOCl}_2$ . It is easy to move *down* the hierarchy of reactivity (see Table 4.1) and fortunately esters and amides, which are at the bottom, are the acid derivatives most usually required.

**Table 4.1** Hierarchy of reactivity for acid derivatives



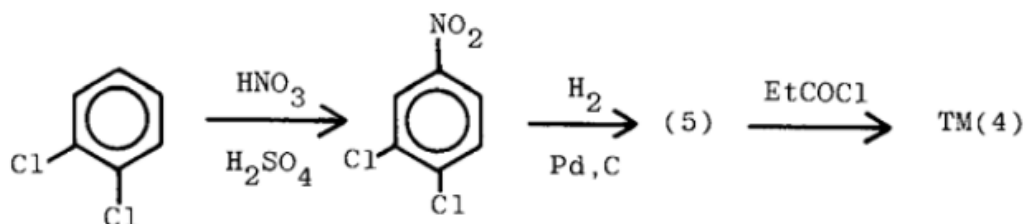
The weedkiller Propanil (4) used in rice fields<sup>33</sup> is an amide so we disconnect to an amine and an acid chloride. Further disconnection of the aromatic amine (5) follows from Chapters 2 and 3.

Propanil: *Analysis*



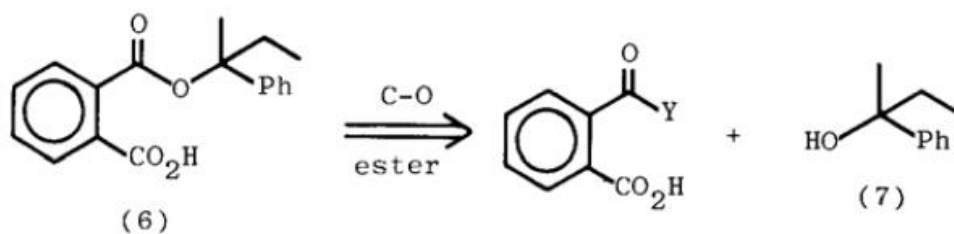
The orientation for nitration is correct: steric hindrance will prevent formation of much 1,2,3-trisubstituted compound.

### Synthesis

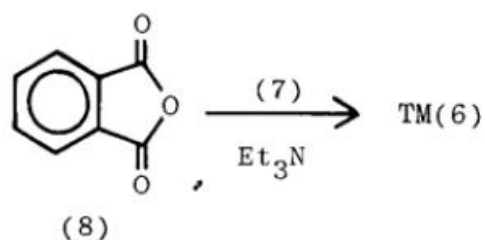


Compound (6) is a more complicated example but we can recognise an ester which we can disconnect in the usual way, simplifying the problem greatly. The very cheap phthalic anhydride (8) is the best acid derivative here and the synthesis of the alcohol (7) is discussed in Chapter 10.

### Analysis



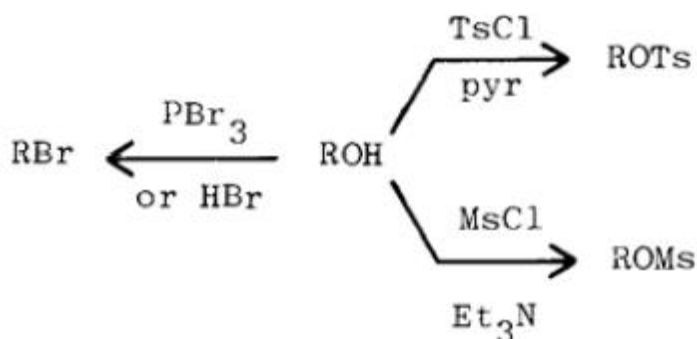
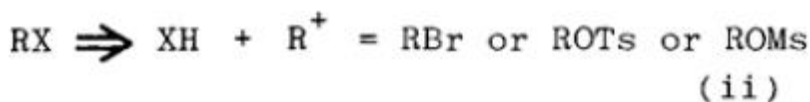
### Synthesis<sup>34</sup>



This molecule (6) was needed for the resolution of alcohol (7) into optical isomers, a derivative with an ionisable group (here CO<sub>2</sub>H) being required.

## Alcohols, Ethers, Alkyl Halides, and Sulphides

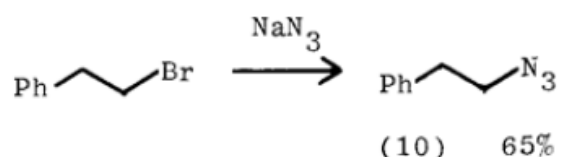
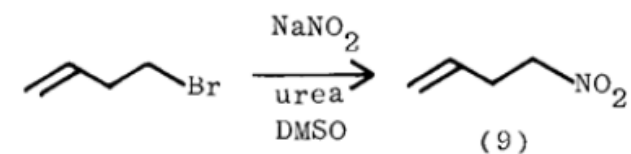
C-X disconnection in aliphatic compounds (ii) gives a nucleophile XH and an electrophilic carbon species usually represented by an alkyl halide, tosylate\*, or mesylate\*. These compounds can all be made from alcohols (ii) and as alcohols can be made by C-C bond formation (Chapter 10) we shall treat the alcohol as the central functional group (Table 4.2).



**Table 4.2** Aliphatic compounds derived from alcohols

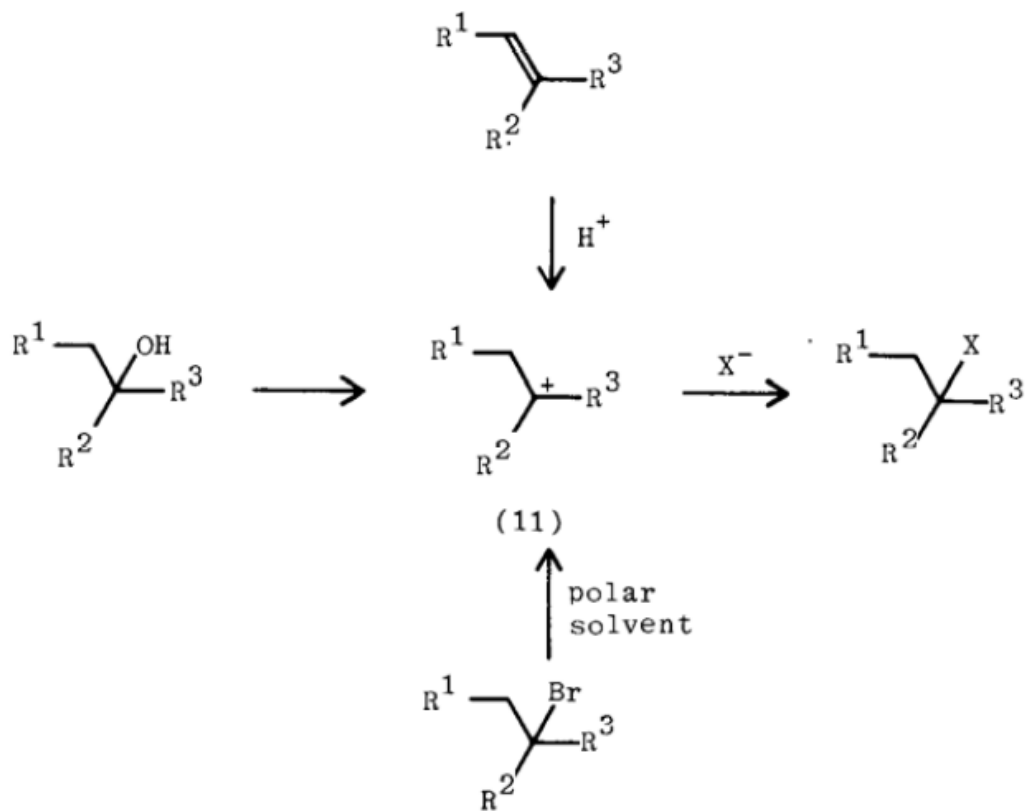
$ROH \rightleftharpoons RX$ $X = \text{halide}$ $OTs, OMs$	$R'OH$ base	$ROR'$	Ethers
	$R'SH$ base	$RSR'$	Sulphides
	1. $(NH_2)_2CS$ 2. $HO^-/H_2O$	$RSH$	Thiols
	$Hal^-$	$RHal$	Alkyl halides
	$Nu$	$RNu$	Other derivatives

Conditions must be chosen to suit the structure of the molecules. Methyl and primary alkyl derivatives react by the  $S_N2$  mechanism so powerful nucleophiles and non-polar solvents are effective. The nitro compound<sup>35</sup> (9) and the azide<sup>36</sup> (10)—examples of the ‘other derivatives’ in Table 4.2—are easily made from the corresponding bromides by  $S_N2$  reactions as they are both primary alkyl compounds.



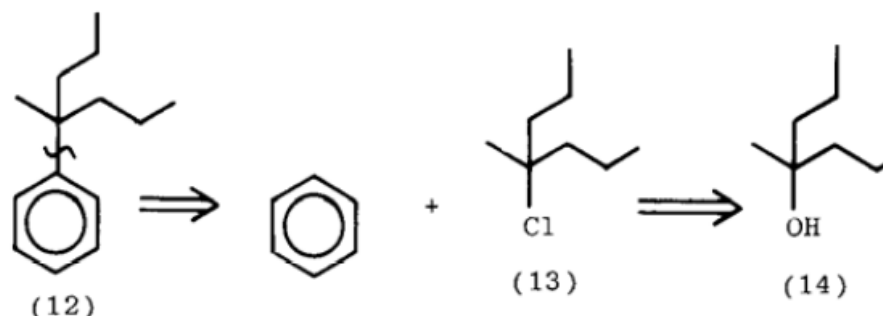
Tertiary compounds react even more easily by the  $S_N1$  mechanism *via* stable carbonium ions (11) generated directly from alcohols, alkyl halides, or even

alkenes. Powerful nucleophiles are no help here but polar solvents and catalysis (usually acid or Lewis acid) help by making the OH a better leaving group.



Compound **(12)** can obviously be made by a Friedel–Crafts reaction from benzene and the tertiary chloride **(13)**, which comes from the alcohol **(14)**. The only reagent needed for **(14)** → **(13)** is conc. HCl. The synthesis of compounds like **(14)** is discussed in Chapter 10.

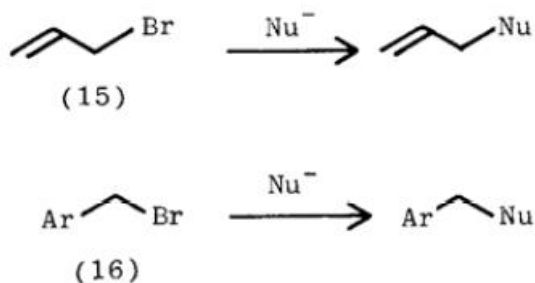
*Analysis*



*Synthesis*<sup>37</sup>



Allylic **(15)** and benzylic **(16)** derivatives react easily both by  $S_N1$  and  $S_N2$  mechanisms so conditions are relatively unimportant here. By contrast, secondary alkyl derivatives are the most difficult to make and conditions need to be rather harsh in these cases.



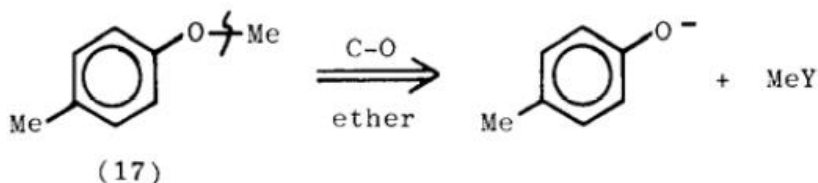
These interconversions are rather elementary in concept but are essential to synthetic planning. Compounds of the type  $R^1-X-R^2$  offer a choice for the first disconnection and are more interesting.



## Ethers and Sulphides

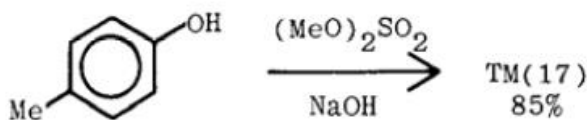
We can often choose our first disconnection because of the reactivity (or lack of it) of one side of the target molecule. The oxygen atom in the wallflower perfume compound (**17**) has a reactive side (Me, by  $S_N2$ ) and an unreactive (Ar) side so disconnection is easy.

### Analysis



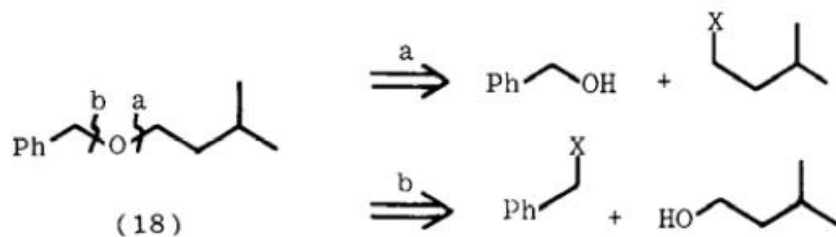
Dimethyl sulphate is used for methylation of phenols in alkaline solution where the phenol is ionised. Since the mechanism is  $S_N2$ , the more powerfully nucleophilic anion is an advantage.

### Synthesis<sup>38</sup>



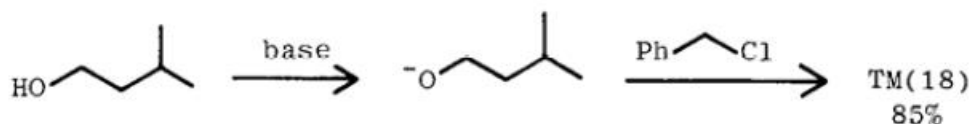
The gardenia perfume compound (**18**) can be disconnected on either side as both involve primary alkyl halides. The benzyl halide is more reactive but the decisive point in favour of route (b) is that route (a) might well lead to elimination.

### Analysis



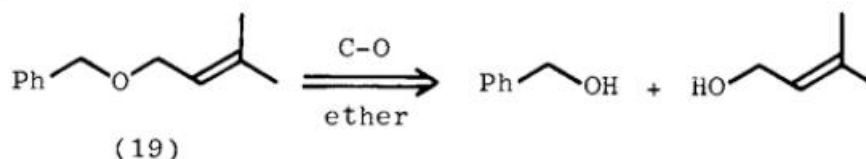
### Synthesis

This is  $S_N2$  again, so base catalysis helps.<sup>39</sup>

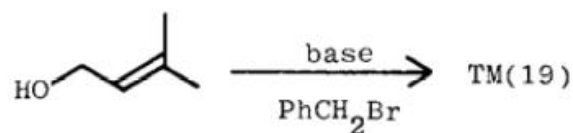


If there is no obvious preference, it is more helpful to write both fragments as alcohols and decide later which to convert into an electrophile. Baldwin<sup>40</sup> needed the ether (19) to study the rearrangement of its carbanion. Both sides are reactive so we write the two alcohols. Baldwin does not reveal<sup>40</sup> how he actually made the ether (19)—both routes look good, although the one shown is less ambiguous.

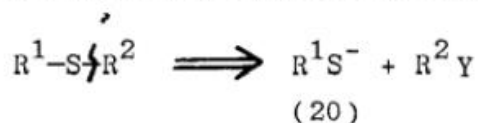
### Analysis



### Synthesis

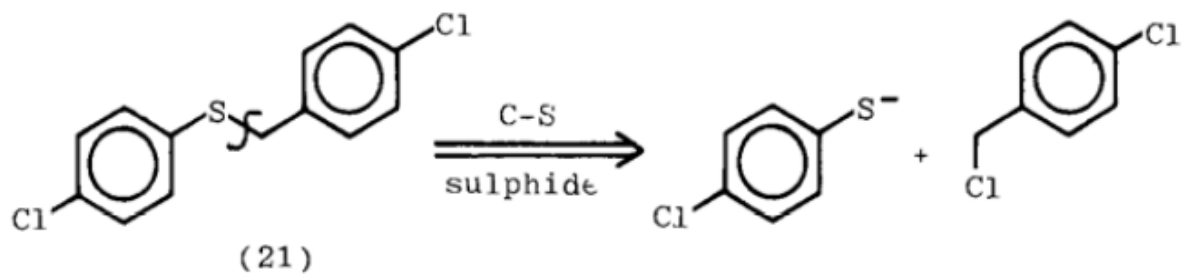


The same principles apply to sulphide ( $R^1SR^2$ ) synthesis. The reaction is even easier by  $S_N2$  as thiols ionise at a lower  $pK_a$  than alcohols, the anion (20) is softer than  $RO^-$  and thus more nucleophilic towards  $sp^3$  carbon.



The acaricide (kills mites and ticks) Chlorbenside (21) is first disconnected on the alkyl rather than the aryl side. The synthesis of thiols is discussed in the next chapter.

### Chlorbenside: Analysis



*Synthesis*<sup>41</sup>

