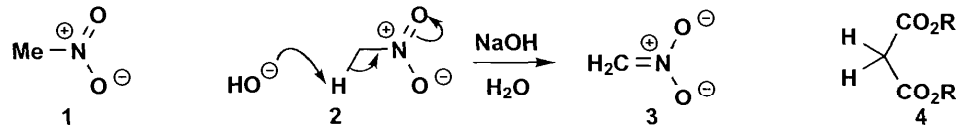
22 Strategy X: Aliphatic Nitro Compounds in Synthesis

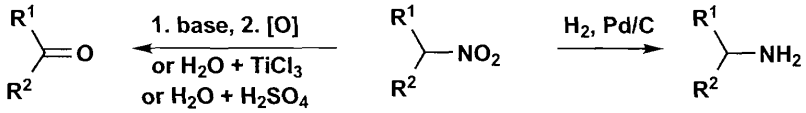
Background Needed for this Chapter Reference to Clayden, *Organic Chemistry:* Chapter 26: Alkylation of Enolates.

In chapter 21 we mentioned nitro compounds as promoters of conjugate addition: they also stabilise anions strongly but do not usually act as electrophiles so that self-condensation is not found with nitro compounds. The nitro group is more than twice as good as a carbonyl group at stabilising an 'enolate' anion. Nitromethane (pK_a~10) **1** has a lower pK_a than malonates **4** (pK_a~13). In fact it dissolves in aqueous NaOH as the 'enolate' anion **3** formed in a way **2** that looks like enolate anion formation.



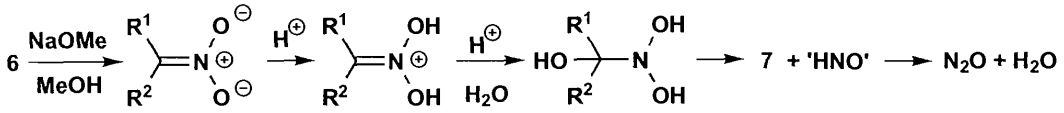
1 2 3 4

Few aliphatic nitro compounds are wanted as target molecules in their own right but the nitro group is important in synthesis because it can be converted into two functional groups in great demand: amines **7**, by reduction, and ketones **5**, by various forms of hydrolysis.



5 6 7

The reduction is straightforward: the N-O bond is weak and is reduced by catalytic hydrogenation but the 'hydrolysis' needs some comments. Early and violent methods included the Nef reaction[1]—the hydrolysis of the 'enol' form **8** in strong acid, probably via the intermediate **10** with liberation of nitrous oxide N_2O.

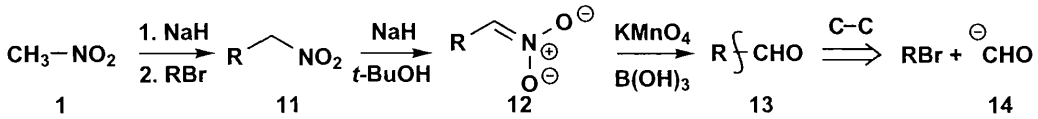


8 9 10

Organic Synthesis: The Disconnection Approach. Second Edition Stuart Warren and Paul Wyatt

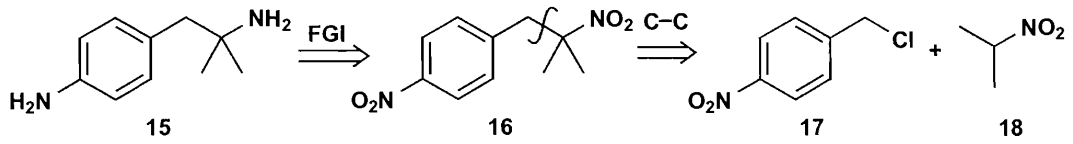
Strangely enough other methods use either oxidation or reduction. The anion **8** can be oxidised at the C=N double bond by ozone[2] or $KMnO_4$ (permanganate).[3] On the other hand, the imine formed by reduction of the N–O bonds, can be hydrolysed to the ketone. It seemed that $TiCl_3$ was the solution to these problems as the McMurry reaction[4] gives excellent yields of ketones. But the recent surge in price of all Ti(III) salts has made this less attractive.

Nitro compounds can be alkylated and are good at conjugate addition (chapter 21) so the products of these reactions can be used to make aldehydes, ketones and amines. A simple synthesis of octanal[5] shows that these methods can work very well indeed. Alkylation of nitromethane with bromoheptane gives the nitro-compound **11**. Formation of the anion **12** and oxidation with $KMnO_4$ gives octanal in 89% yield. This chemistry gives us the disconnection to an alkyl halide and a carbonyl anion. The anion **12** is an 'acyl anion equivalent' and we shall need these in the next chapter.

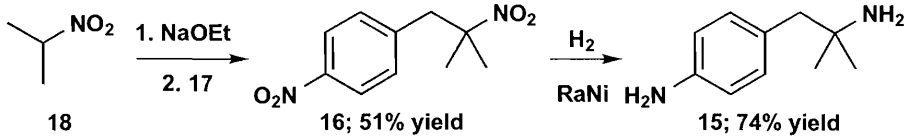


Reduction of Nitro Compounds

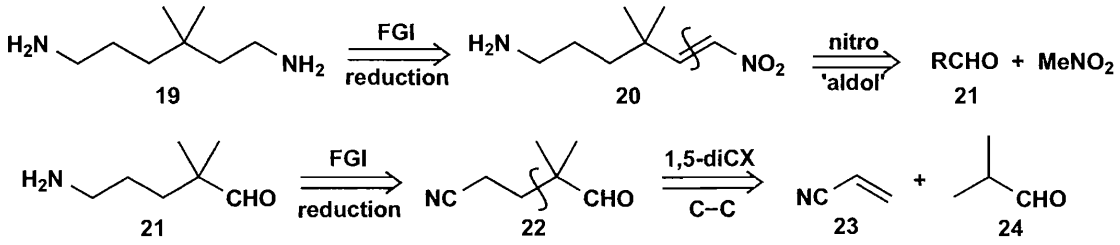
The sequence of alkylation followed by reduction gives an amine and the special advantage of this strategy is that it can lead to *t*-alkyl amines. The appetite suppressant **15** can be disconnected next to the tertiary centre after the amines are changed to a nitro-compound **16**. 2-Nitropropane **18** is available.



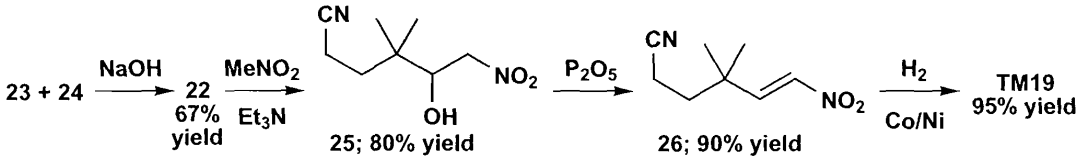
The synthesis uses alkylation by a benzylic halide and the reduction of both nitro groups is done catalytically with Raney nickel in the same step.[6]



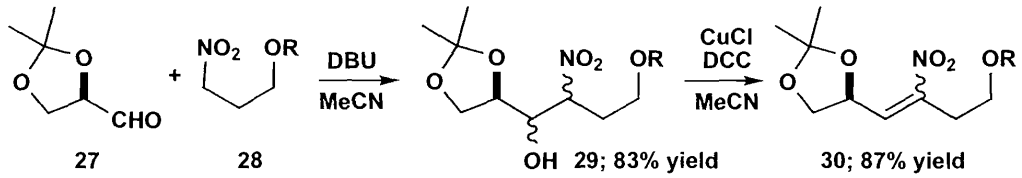
Other groups beside nitro can be reduced in the same step. So the diamine **19**, needed for polyamine manufacture, could come from the unsaturated nitro compound **20** that would in turn come from an 'aldol' reaction between the anion of nitromethane **1** and the aldehyde **21**. This has a 1,5-diX relationship and acrylonitrile **23** is excellent at conjugate addition (chapter 21) so we can use isobutyraldehyde **24** as a starting material.



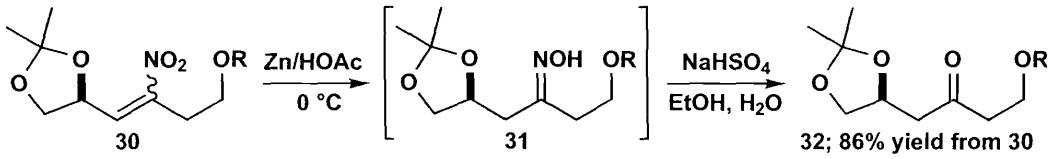
In the synthesis we should not wish to make **21** as it would cyclise and, in any case, we'd rather reduce nitrile, nitro and alkene all in the same step by catalytic hydrogenation. The very simple method used for the conjugate addition is possible only because of the slow aldol reaction of the hindered aldehyde **24**. The 'aldol' **25**, also called a Henry reaction, needs a separate dehydration step but the three functional groups in **26** are reduced in one step in good yield.[7]



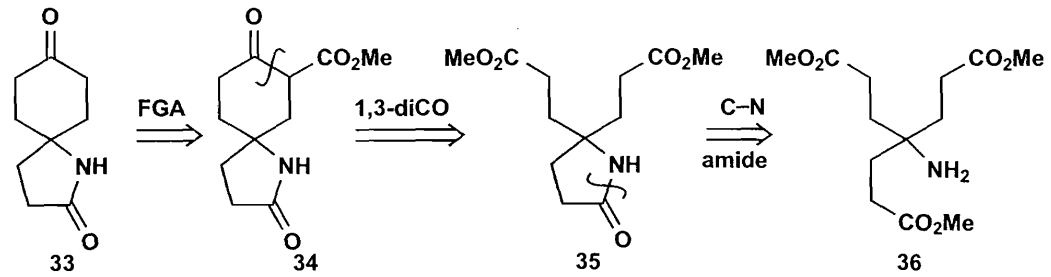
The 'nitro-aldols' can also be converted to ketones. The enantiomerically pure aldehyde **27** (a protected form of glyceraldehyde) reacts with **28** to give the 'aldol' **29** as a mixture of diastereoisomers. The protecting group 'R' is the very hindered TIPS group $(i\text{-Pr})_3Si$. Dehydration by DCC catalysed by Cu(I) gives the nitroalkene **30** as an E/Z mixture.



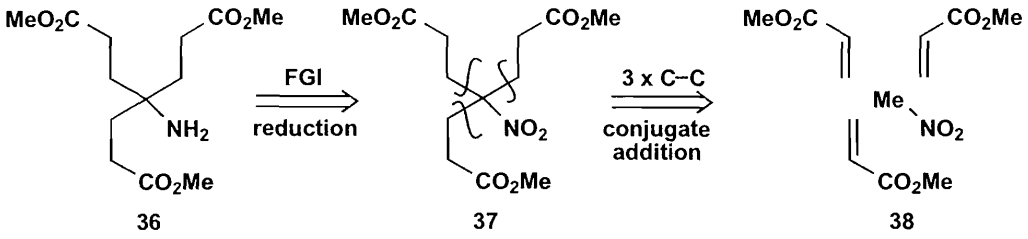
Reduction of **30** with the mild reducing agent Zn/HOAc at 0 °C gives the oxime **31** that can be hydrolysed directly to the ketone **32** without isolation.[8] This ketone was used in a synthesis of compactin.[9]



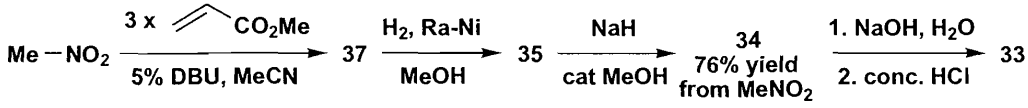
Nitro-alkanes are good at conjugate additions too. In a synthesis of an immunosuppressant for organ transplants, the spirocyclic amido-ketone **33** was needed. As this is a symmetrical ketone we can use the strategy of adding an ester group and then a 1,3-diCO disconnection **34** to give symmetrical **35**. You might have disconnected the amide first but whenever you do it, you should expose an even more symmetrical compound **36**. Can we use this symmetry?



If we change the amine in **36** to a nitro group **37**, three conjugate additions of methyl acrylate to nitromethane become a possibility. Though you need quick thinking to see this, all the disconnections are ones we have seen before.

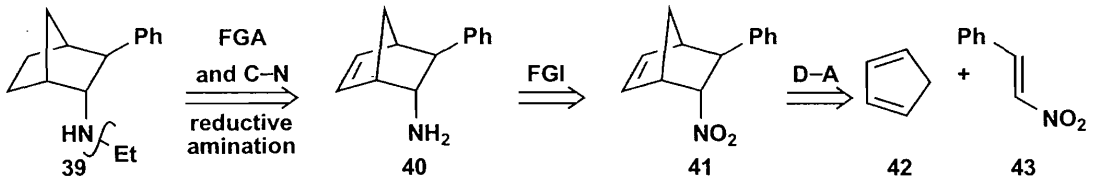


The synthesis is of course very short.[10] Three equivalents of methyl acrylate add to nitromethane with catalytic (5%) DBU to give the adduct **37** and reduction leads to spontaneous cyclisation of one of the ester groups to give **35**. The rest is as planned.

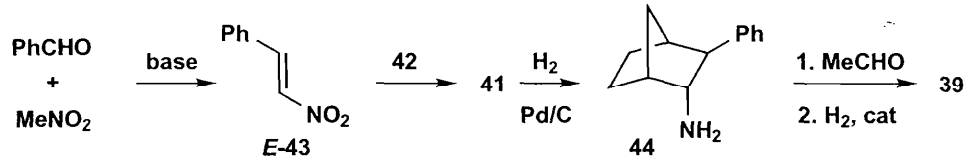


Diels-Alder Reactions

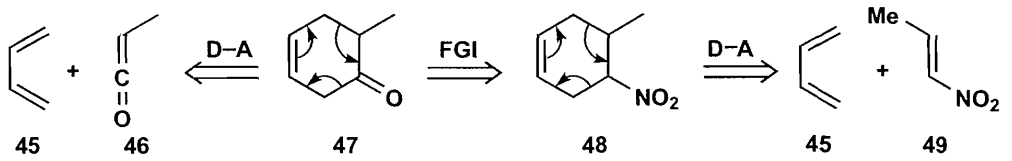
Nitroalkenes (see **30**) are easily made from nitro-alkanes and aldehydes and take part as dienophiles in Diels-Alder reactions (chapter 17). The products can, as usual, be converted into amines or ketones. The stimulant fencamfamin **39** disconnects to the obvious Diels-Alder adduct **41** from cyclopentadiene **42** and the nitro-alkene **43**.



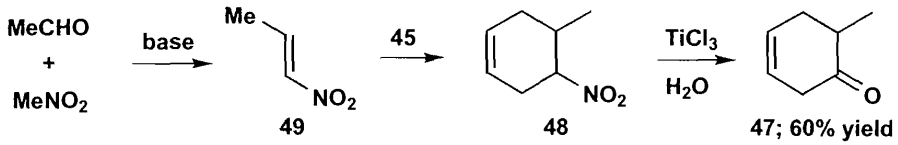
The synthesis starts as planned and catalytic hydrogenation reduces both the alkene and the nitro group in one step to give **44**. In the reductive amination, the imine can be formed and then hydrogenated.[11]



Now, how about making the ketone **47** by the Diels-Alder reaction? Direct disconnection (arrows on **47**) leads to a good diene **45** but an unacceptable dienophile **46**. This is a ketene and they don't do Diels-Alder reactions. You will see in chapter 33 what they can do. But if you change the ketone into a nitro group **48**, the problem disappears.



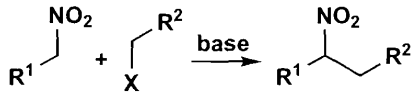
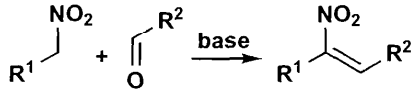
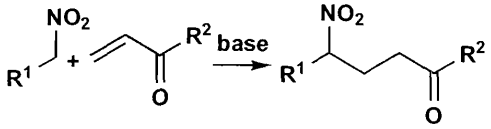
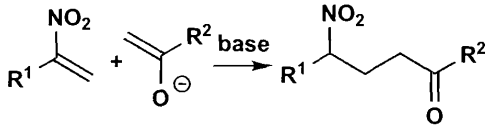
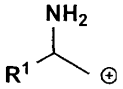
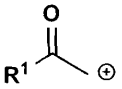
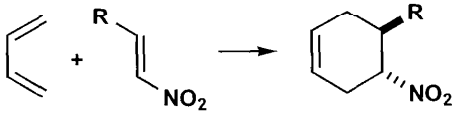
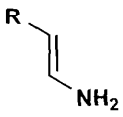
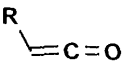
This is the work of McMurry so you can expect him to use his reagent ($TiCl_3/H_2O$) to convert the nitro group into the ketone **47**. The stereochemistry of the Diels-Alder adduct **48** is of no interest as both diastereomers give[2] **47**.



Summary of Nitro Groups in Synthesis

The nitro group is remarkably versatile and solves otherwise difficult problems. The table is meant to help you see which synthons can be represented by nitro-compounds. Note particularly that the charged synthons all have unnatural polarity and the primary enamine in the Diels-Alder entry could not be made without protection of the amine.

TABLE 22.1 Synthons represented by the nitro group

Reaction	Example	Synthon Represented	
		if reduced	if ketone made
Alkylation			
Nitro 'aldol'			
Conjugate addition			
Conjugate addition with nitro alkenes			
Diels-Alder			

References

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