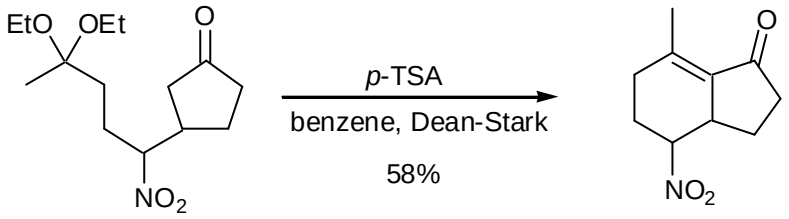
Chapter IX: Transformation of the Michael adducts

1 Cyclization

1.1 Literature survey

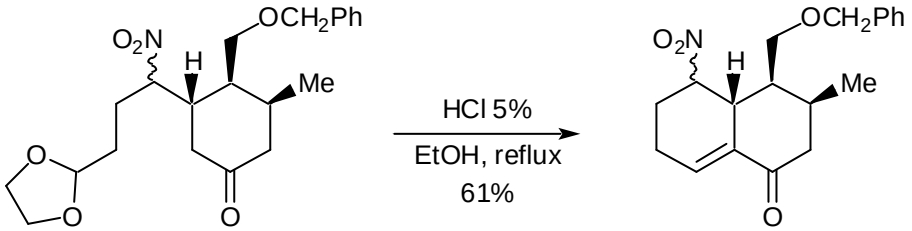
We have already shown that nitro-compounds have been used as pentannulation reagents by Toke (scheme 118)[183] and by Hoffmann (scheme 119).[185] Cyclizations were carried out in acidic conditions. Michael adduct **212** was refluxed in benzene in a Dean-Stark apparatus in the presence of para-toluenesulfonic acid to yield the cyclization product **213** (scheme 160).[229]



212 **213**

Scheme 160

Hoffmann used aqueous sulfuric acid to realize the cyclization (scheme 119).[185] Another example using nitro-compounds was given by Barco *et al.*.[230] They refluxed Michael adduct **214** in ethanol in the presence of dilute hydrochloric acid to form compound **215** (scheme 161).

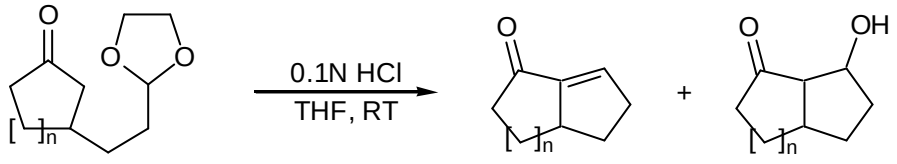


214 **215**

Scheme 161

[229] Kádas, I.; Árvai, G.; Töke, L.; Toth, G.; Szollosy, A.; Bihari, M. *Tetrahedron*, **1994**, *50*, 2895-2906.
[230] Barco, A.; Benetti, S.; Bianchi, A.; Casolari, A.; Pollini, G. P.; Romagnoli, R.; Spalluto, G.; Zanirato, V. *Tetrahedron*, **1994**, *50*, 11743-11754.

Other methods that could be applied to the cyclization have been published. Thus Helquist described the use of a catalytic amount of hydrochloric acid in THF at room temperature to cyclize adduct **216** (scheme 162).[231]



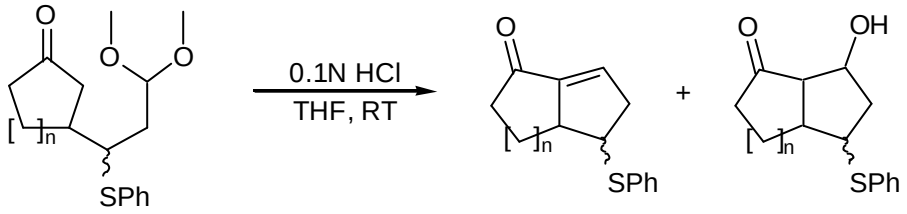
216

n = 1	0	54%
n = 2	89%	0%
n = 3	80%	0%

Scheme 162

It is interesting to note that upon cyclization dehydration occurred except in the case of cyclopentenone (n = 1).

The same observation was made by P. Ding in our laboratory. Cyclization of **217** was realized by the use of a small amount of concentrated hydrochloric acid in THF. Whereas cyclohexanone and cycloheptanone led to the dehydrated product cyclopentanone furnished a β-hydroxyketone (scheme 163).[232]



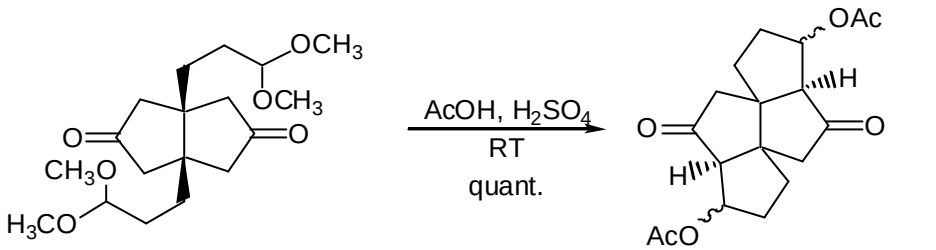
217

n = 1	0	40%
n = 2	81%	0%
n = 3	77%	0%

Scheme 163

In the same manner the cyclization product of a five-membered ring could be obtained by the use of a mixture of acetic acid and sulfonic acid (scheme 164).[233]

[231] Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.*, **1982**, *47*, 5045-5050.
[232] Ding, P.; Ghosez, L. *Tetrahedron*, **2002**, *58*, 1565-1571.
[233] Venkatachalam, M.; Deshpande, M. N.; Jawdosiuk, M.; Kubiak, G.; Wehrli, S.; Cook, J. M.; Weiss, U. *Tetrahedron*, **1986**, *42*, 1597-1605.



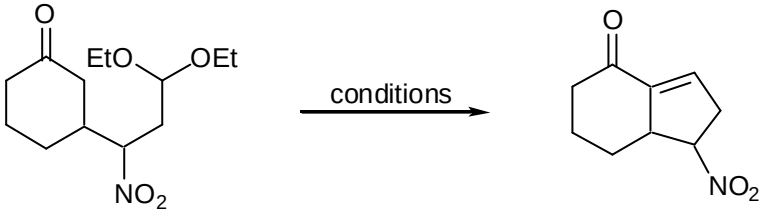
cic-cis : *trans-trans* 75 : 25

Scheme 164

1.2 Cyclization catalyzed by a Brønsted acid

We tried the cyclization of **186** in various conditions using different solvents, quantities of acid and / or temperature (table 47).

Table 47: *Attempts to the cyclization of **186.***



186 **218**

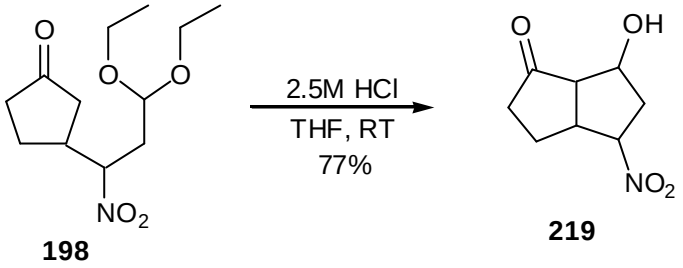
Entry	Conditions	Yield	Remarks
1	HCl 5% : 1,4-dioxane (1 : 1), reflux, 4h[234]	0%	degradation
2	HCl 5% : 1,4-dioxane (1 : 1), RT, 4h	0%	starting material
3	AcOH, RT, 5 days	8%	+ starting material
4	AcOH, 4 drops of H_2SO_4, RT, 5 days[233]	15%	+ starting material and degradation
5	HCl 0.1M : THF (1 : 10), RT, 5 days[231]	0%	no reaction
6	HCl 12.5M (a few drops), THF, RT, 3h	20.5%	+ 25% starting material
7	pTSA, benzene, Dean-Stark[229]	44%	92% crude yield
8	HCl 2.5M : THF (1 : 30), RT, 2h	0%	quant. crude yield, degradation upon purification
9	HCl 12.5M : THF (1 : 30), RT, 2h[232]	66%	97% crude yield

The best conditions to realize the cyclization reaction were to use a small quantity of more or less concentrated hydrochloric acid (>2.5M) in THF or *para*-toluensulfonic acid in a Dean-Stark apparatus (entries 6-9). The major problem with

[234] Momose, T.; Yoshizawa, E.; Muraoka, O. *Synth. Commun*, **1985**, *15*, 17-25.

this reaction seemed to be the stability of product **218**. Good yields of crude product were indeed obtained (entries 7-9), but yields always dropped upon purification.

Adduct **198** was cyclized in the conditions described in entry 8. The bicyclic compound **219** was obtained in good yield as a mixture of 2 diastereomers that could be separated by flash chromatography (scheme 165).

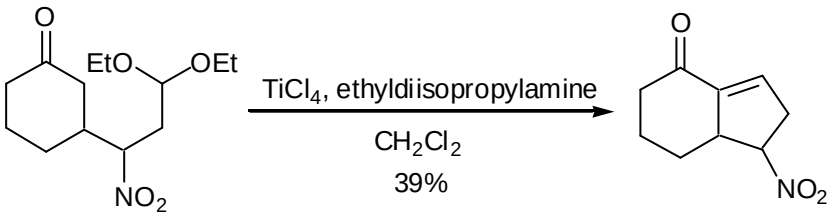


198 **219**

Scheme 165

1.3 Cyclization using a Lewis acid

We also tried a method described by Evans for a related reaction[235] using titanium tetrachloride and ethyldiisopropylamine (scheme 166). The desired compound **218** was obtained in 39% yield, but contaminated with 19% of **186** and a significant amount of side-product.



186 **218**

Scheme 166

This method was no improvement compared to the others. We did therefore not investigate it further.

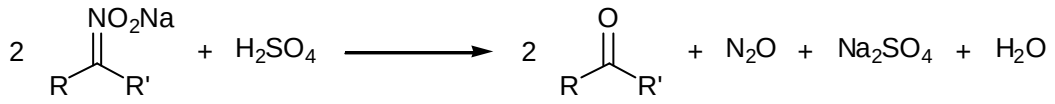
2 Nef reaction

2.1 Literature survey

The Nef reaction is the transformation of a CH-NO_2 group into a carbonyl group.[236] Treatment of nitro salts with an acid resulted in the hydrolysis to a carbonyl

[235] Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.*, **1990**, *112*, 8215-8216.
[236] Nef, J. U. *Liebigs Ann. Chem.*, **1894**, *280*, 264.

group. Primary and secondary nitro compounds could thus be transformed into aldehydes and ketones respectively (scheme 167).

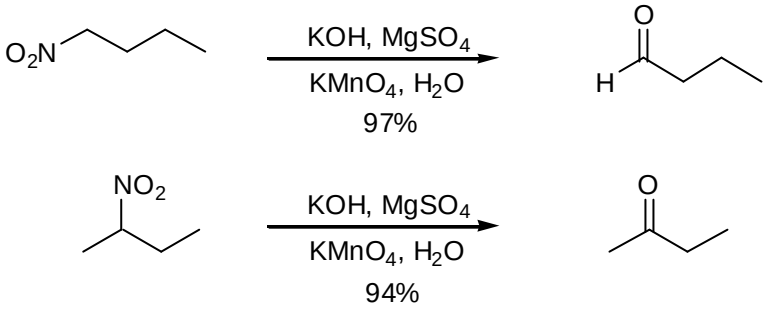


Scheme 167

The harsh conditions of this reaction make it unsuitable for sensitive compounds and a large number of variations have been described since.

2.1.1 The Nef reaction in oxidative conditions

A major amelioration has been achieved by the use of oxidative conditions. Shechter has shown that potassium permanganate could advantageously been used to transform nitro compounds into carbonyls (scheme 168).[237] The reaction was carried out in the presence of potassium hydroxide and magnesium sulfate.



Scheme 168

Kornblum used sodium *tert*-butoxide, formed *in situ* by action of sodium hydride on *tert*-butanol, as base.[238] Another modification was made by Clark who used supported permanganate to perform the Nef reaction.[239] Potassium permanganate was reacted with silicagel to form the supported permanganate. Another modified method was developed by Chandrasekaran who realized Nef reactions with cetyltrimethylammonium permanganate.[240]

Other oxidants than permanganate have been used. Bartlett for example has shown that *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ allowed to transform sensitive nitro compounds into carbonyl derivatives (scheme 169).[241]

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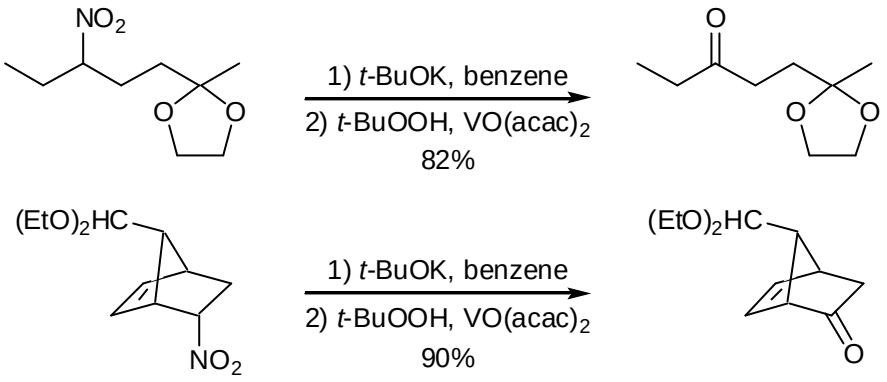
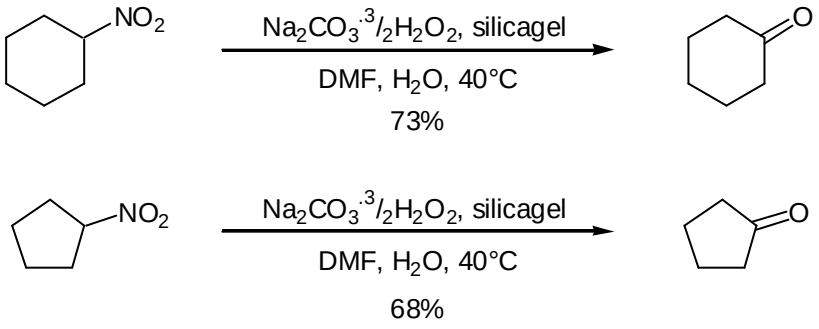
[237] Shechter, H.; Williams Jr., F. T. *J. Org. Chem.*, **1962**, *27*, 3699.
[238] Kornblum, N.; Erickson, A. S.; Kelly, W. J.; Henggeler, B. *J. Org. Chem.*, **1982**, *47*, 4534.
[239] Clark, J. H.; Cork, D. G. *J. Chem. Soc. Perkin Trans. 1*, **1983**, 2253-2258.
[240] Vankar, P. S.; Rathore, R.; Chandrasekaran, S. *Synth. Commun*, **1987**, *17*, 195.
[241] Bartlett, P. A.; Green III, F. R.; Webb, T. R. *Tetrahedron Lett.*, **1977**, 331.



Scheme 169

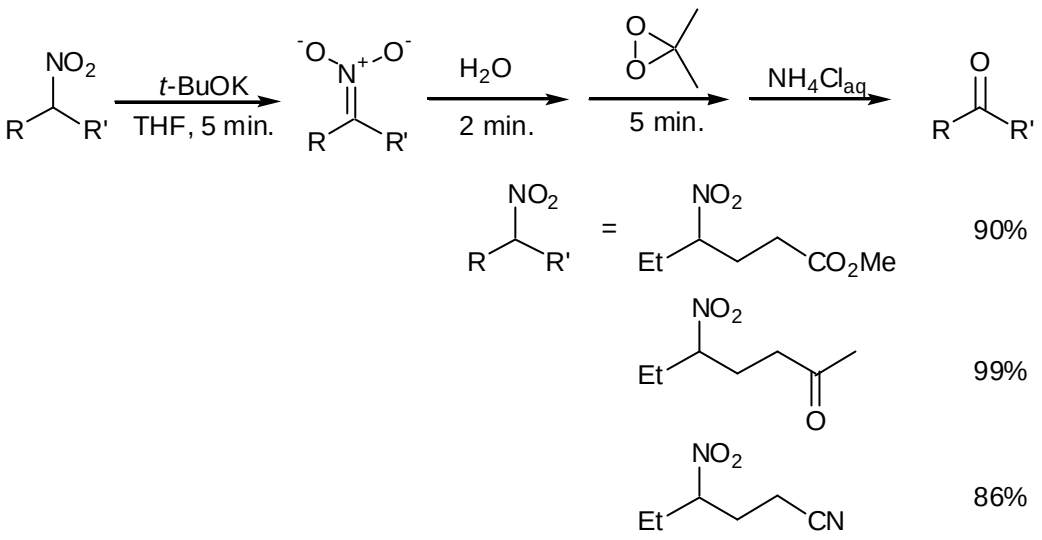
Sodium percarbonate has also been proven to be an efficient reagent for the Nef reaction when used in the presence of silicagel (scheme 170).[242] Without silicagel the same reaction was also possible but took 12 to 15 hours instead of 1 hour.



Scheme 170

A last set of conditions is the use of dimethyldioxirane (DMD).[243] Nitro compounds, after being transformed to the anion, reacted with DMD to give the corresponding ketone (scheme 171).

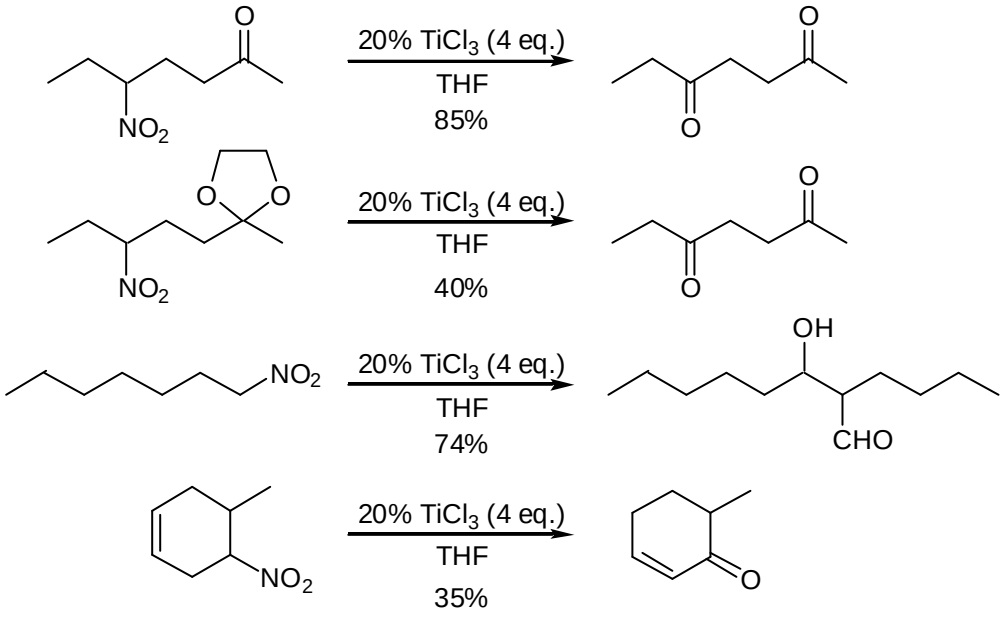
[242] Narayana, C.; Reddy, N. K.; Kabalka, G. W. *Synth. Commun*, **1992**, *22*, 2587.
[243] Adam, W.; Makosza, M.; SahaMoller, C. R.; Zhao, C. G. *Synlett*, **1998**, 1335.



Scheme 171

2.1.2 Nef reaction in reductive conditions

Instead of oxidizing the nitronate it can also be reduced to an imine which is subsequently hydrolyzed to a carbonyl. The most often used method has been developed by McMurry.[244] Aqueous titanium trichloride solution allowed to realize the Nef reaction, but due to the high acidity (pH < 1) other reactions occurred: hydrolysis of ketals, aldolisation or double bond migration (scheme 172).

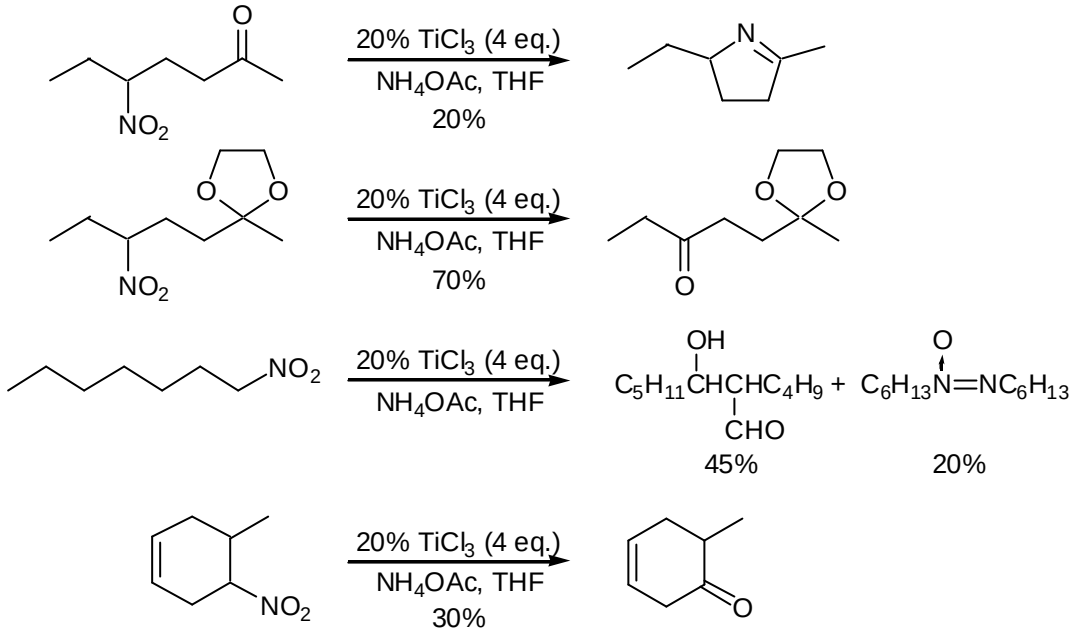


Scheme 172

However when titanium trichloride was used in a buffered (pH = 6) medium all these side reactions, except for the aldolization, could be avoided (scheme 173).

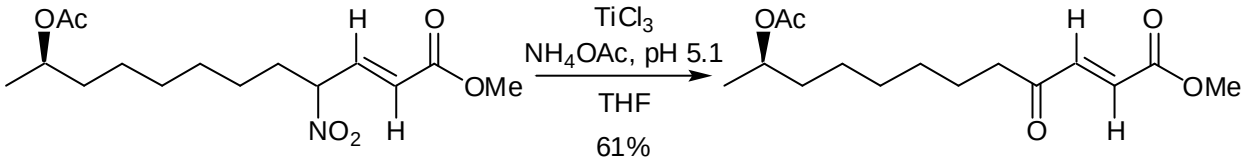
[244] McMurry, J. E.; Melton, J. *J. Org. Chem.*, **1973**, *38*, 4367.

Interestingly 5-nitroheptan-2-one did not lead to the diketone but cyclized to form an imine.



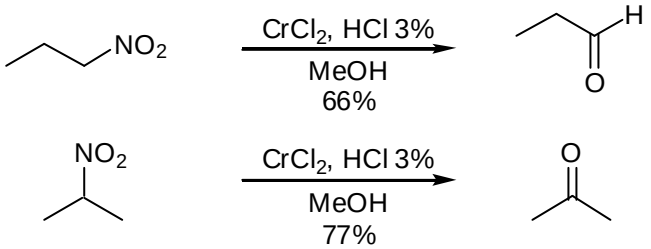
Scheme 173

Application of this method to sensitive compounds is possible. An example was given by Barua in the total synthesis of *R*-(-)-patulolide A (scheme 174).[245]



Scheme 174

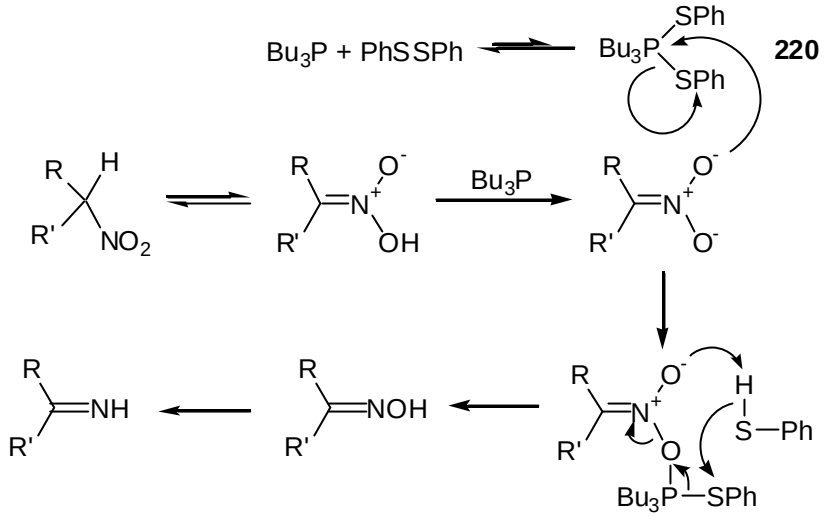
Another reducing agent is chromium (II) chloride.[246] Simple nitroalkanes were readily reduced into ketones or aldehydes (scheme 175). Drawbacks of this method were acidic conditions and the use of 15 equivalents of reducing agent.



Scheme 175

[245] Kalita, D.; Khan, A. T.; Barua, N. C.; Bez, G. *Tetrahedron*, **1999**, *55*, 5177.
[246] Akita, Y.; Inaba, M.; Uchida, H.; Ohta, A. *Synthesis*, **1977**, 792.

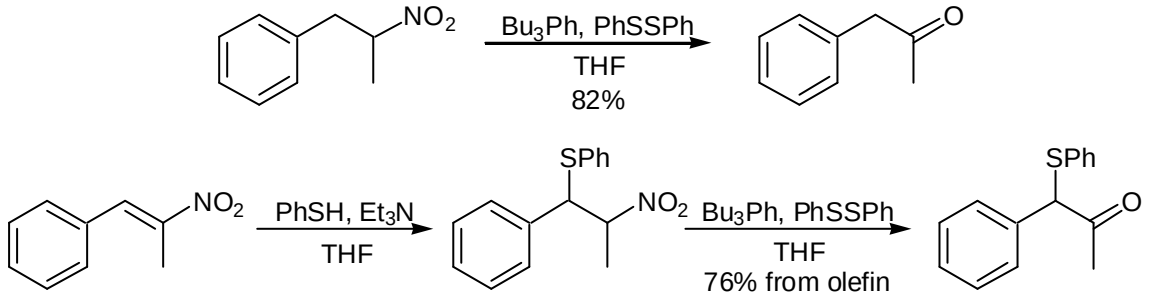
A reductive method that did not use a metal has been described by Barton and Zard.[247] The reaction was carried out by the use of tributylphosphine and diphenyldisulfide. The mechanism is supposed to be as described in scheme 176.



Scheme 176

On one side tributylphosphine reacted with diphenyldisulfide to form phosphorane **220**. On the other side a nitronate anion could be formed by the mildly basic phosphine. **220** reacted with the anion, finally collapsing to an imine which was hydrolyzed to a ketone by the use of water. The driving force of the reaction could be the formation of the P,O-double bond.

The Nef reaction was realized with good yields (scheme 177).



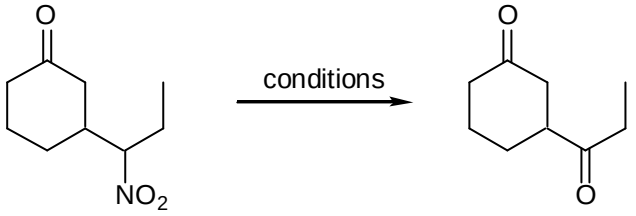
Scheme 177

2.2 Results

We began our study with compound **178**. Different reaction conditions were tested. Results are summarized in table 48.

[247] Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 2243-2252.

Table 48: *Nef reaction of **178** under various conditions.*



178 **221**

Entry	Conditions	Yield	Remarks
1	$CrCl_2$, HCl_{aq}, MeOH, 2h[246]	89%	
2	H_2O_2, K_2CO_3, MeOH, H_2O, 23h[248]	35%	+35% starting material
3	1) NaOH, $MgSO_4$, H_2O 2) $KMnO_4$[237]	-	Very low conversion (<10%)
4	$TiCl_3$ (4 eq.), NH_4OAc, DME, H_2O[244]	20%	No starting material
5	$TiCl_3$ (16 eq.), NH_4OAc, DME, H_2O[244]	26%	No starting material
6	$Na_2CO_3 \cdot {}^3/_2H_2O_2$, SiO_2, DMF, H_2O, 40°C, 1h[242]	0%	Starting material
7	1) Bu_3Ph, PhSSPh, THF 2) H_2O[247]	52%	+13% starting material

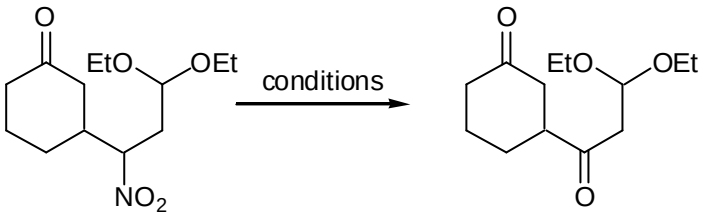
Not all the conditions described in the literature gave the expected result. No or nearly no reaction was observed when using potassium permanganate (entry 3) or sodium percarbonate (entry 6). The use of titanium trichloride resulted in only low yield (entries 4-5). We thought it could be due to the age of the reagent, but even a freshly opened bottle did not improve the result. Oxidation by hydrogen peroxide (entry 2) or reduction by tributylphosphine (entry 7) resulted in only modest yield. Starting materiel could be recovered in all the cases except the conditions described by McMurry.

The best result was obtained by using chromium dichloride (entry 1). Diketone **221** was obtained in good yield as pure product without purification. Unfortunately these were the less ecologically friendly conditions.

We then applied some of these conditions to the Nef reaction of **186** (table 49).

[248] Jonsson, S. Y.; Löfström, C. M. G.; Bäckvall, J.-E. *J. Org. Chem.*, **2000**, *65*, 8454-8457.

Table 49: *Nef reaction of **186** under various conditions.*



186 **222**

Entry	Conditions	Yield	Remarks
1	$CrCl_2$, HCl_{aq}, MeOH, 2h[246]	-	Unidentified product
2	H_2O_2, K_2CO_3, MeOH, H_2O, 23h[248]	0%	Starting materiel
3	$TiCl_3$ (16 eq.), NH_4OAc, DME, H_2O[244]	16%	81% crude yield
4	1) Bu_3Ph, PhSSPh, THF 2) H_2O[247]	67%	

The reaction with chromium dichloride did not allow us to obtain the desired compound (entry 1). No reaction was observed with hydrogen peroxide did (entry 2). With titanium trichloride the reaction proceeded well but we had problems with the purification of the product (entry 3). The best conditions were therefore the use of tributylphosphine and diphenyldisulfide which permitted to obtain diketone **222** in acceptable yields.

3 Conclusion

In this chapter we have shown that the Michael adducts could easily be transformed. The cyclization occurred under acidic conditions to yield the desired bicyclic compounds. The nitro-group could also be removed under mild conditions to yield the corresponding ketone.