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Olefination of 3-diazopiperidin-2-one

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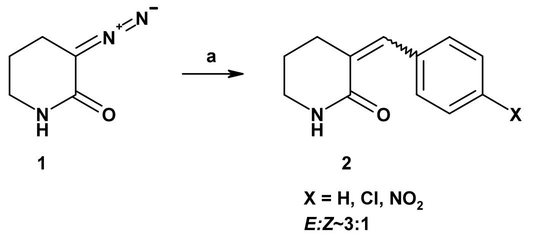
Abstract—New conditions have been developed for the olefination of diazo compounds catalysed by methyl trioxorhenium. The new system is suitable for unreactive diazo compounds and its utility is demonstrated by the olefination of 3-diazopiperidin-2-one with a range of aromatic, heterocyclic and alkylaldehydes.

Diazo compounds are useful synthetic intermediates which have found a wide range of use in organic synthesis.[1] We recently reported the synthesis of the new diazo-amide 3-diazopiperidin-2-one **1** and described some of its chemistry.[2] It undergoes most of the usual diazo-group chemistry such as insertion, 1,3-cycloaddition and cyclopropanation reactions in excellent yields, giving rapid access to a wide range of 3-substituted piperidones. However, when we investigated olefination of **1** with benzaldehydes catalysed by methyl trioxorhenium, under the conditions described by Herrmann,[3] the reaction proceeded in moderate yields (<40%) and poor stereoselectivity (E:Z ~ 3:1) (Scheme 1). Furthermore, the reaction failed in our hands, with alkyl aldehydes.

We wanted to expand the utility of this reaction to provide a novel and very direct approach to 3-alkylated-piperidinones, and from these 3-piperidines, by subsequent reduction of the carbonyl group. We now wish to report our work on improving the olefination reaction of 3-diazopiperidin-2-one **1** with a wide variety of aldehydes, including phenyl, heterocyclic and alkylaldehydes. To achieve this we have modified the published reaction conditions of the $MeReO_3$/phosphine catalytic system.



Scheme 1. *Reagents and conditions*: (a) X-Ph-CHO, $MeReO_3$, PPh_3, THF, rt, 7–12 h.

The poor results we reported with the $MeReO_3/PPh_3$ system[2] led us to evaluate the more recently described systems that catalyse the olefination of ethyl diazoacetate with aldehydes. However, we found that both the trichloro oxorhenium[4] and the ruthenium dichloride[5] systems failed to effect olefination of **1** with benzaldehydes. We therefore concentrated on optimising the $MeReO_3$/phosphine catalytic system for the olefination of **1**.

Monitoring the reaction between **1** and 4-nitro-benzaldehyde in the presence of triphenylphosphine catalysed by $MeReO_3$ in THF indicated a complex reaction mixture.[3] The main components of this mixture were identified by LC/MS (Scheme 2). Although the required product **3** ($MH^+ = 233$) was identified as the major component, another product detected in large amounts, was the phosphazine **4** ($MH^+ = 388$). Also seen, as minor side products were the azine **5** ($MH^+ = 261$) and the diazo decomposition product **6** ($MH^+ = 195$). We performed a number of control reactions to determine how these products arose. When the reaction was carried out in the absence of catalyst, **4** was the major component of the reaction mixture together with small amounts of **5**. Performing the reaction in the absence of triphenylphosphine led to detection of **6** only. Presumably the latter product is derived by initial loss of the diazo group to form a carbene intermediate.

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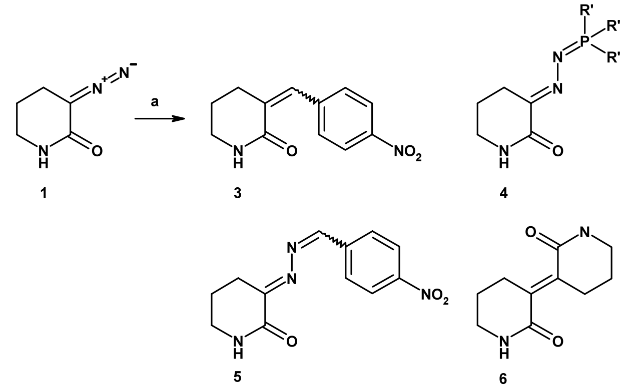
We also noted that the reaction time for olefination of **1** was typically 18 h, whereas the reported reaction times for olefination of ethyl diazoacetate are 2–6 h.[3] It appears that **1** is less reactive under these conditions than ethyl diazoacetate, and this lower reactivity allows several side reactions to occur. Since the major side product **4** arises by direct reaction of the phosphine with the diazo group, we investigated the above olefination reaction (Scheme 2) using $MeReO_3$ with a variety of phosphines (Table 1).

The results show that the only phosphines which gave product **3** and no detectable amounts of side-products **4** or **5** were tris(4-chlorophenyl)phosphine (entry **2**) and diphenyl-2-pyridyl-phosphine (entry **3**). Analysis of the reaction mixture for these two phosphines by LC/MS, indicated a less complex mixture, with the desired product being the major component together with small amounts of **6**. The effect of the phosphines on the outcome of reaction can be rationalised in terms of the steric and electronic properties at the phosphorus atom.[6–8] Thus phosphines which take part in the catalytic cycle leading to olefination have a cone angle <170° (entries **1**–**5**). If this condition is satisfied, side reactions leading to products such as **4** and **5**, can also occur with the more nucleophilic phosphines (entries **1**, **4** and **5**). Phosphines with larger cone angles and high nucleophilicity lead to no reaction (entries **6**–**11**) or to just the side products (entry **12**).



Scheme 2. *Reagents and conditions*: (a) 4-NO_2-Ph-CHO, $MeReO_3$, PR'_3, THF, rt, 24 h.

Table 1. Effect of phosphine on the metal-catalysed olefination of **1**

Entry	PR'_3[a]	Product **3**	Product **4**	Product **5**
1	PPh_3	✓		✓
2	$P(4\text{-Cl-Ph})_3$	✓		
3	$P(2\text{-Py})(Ph)_2$	✓		
4	$P(4\text{-Me-Ph})_3$	✓	✓	✓
5	$P(Benzyl)_3$	✓	✓	
6	$P(2\text{-Me-Ph})_3$			
7	$P(2,4,6\text{-Me-Ph})_3$			
8	$P(2,4,6\text{-MeO-Ph})_3$			
9	$P(2,6\text{-MeO-Ph})_3$			
10	$P(2\text{-furyl})_3$			
11	$P(cyclohexyl)_3$			
12	PBu_3		✓	✓

✓ Product detected in the reaction mixture by LC/MS.

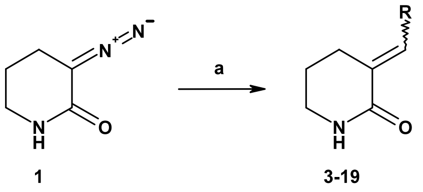
[a] Reactions carried out according to the procedure decribed by Herrmann.[3]

We also investigated the effect of solvent and temperature on the outcome of the reaction. The reaction of 4-nitro-benzaldehyde with **1** was performed using tris(4-chlorophenyl)phosphine and $MeReO_3$ in THF, DCM, $CHCl_3$ and toluene at ambient temperature and at 50°C. Analysis of the reactions after 18 h indicated that the reactions had progressed furthest in DCM and $CHCl_3$ leading to the isolation of product **3** in ~40% yield and with an *E*:*Z* ratio ~10:1. An increase in temperature did not improve the yield in these two solvents. Some of these new conditions[9] were applied to the olefination of **1** with a variety of aldehydes (Scheme 3) and the results are shown in Table 2.

Table 2 shows that by using DCM as the solvent and a less nucleophilic phosphine, we were able to perform the olefination of **1** with alkyl, aryl and heteroaryl aldehydes with overall yields of 20–50%. In addition the stereoselectivity is improved to ~10:1 in favour of the *E* isomer.[10] Some general observations are worthy of note. Yields are best for the more electrophilic aldehydes (compounds **3**, **12**, **13**, **16**). The lowest yields obtained were with the alkyl aldehydes (compounds **17**, **18**, **19**) presumably due to their lower reactivity, which allows more of the side products to compete. One of the lowest yielding reactions was with 2-methylbenzaldehyde (compound **9**) suggesting that steric crowding at the catalytic centre is detrimental to the reaction. Although we found that DCM and $CHCl_3$ are better solvents than THF and toluene for this reaction, yields of reactions carried out in THF could be improved to similar levels by heating to 50°C (compound **10**).

These results demonstrate that olefinations catalysed by $MeReO_3$ can be performed with phosphines other than PPh_3. The two phosphines we have identified are less nucleophilic than the generally used triphenylphosphine in these reactions, and appear to offer an advantage with diazo compounds that can react directly with the phosphine.

We have applied these new conditions to effect olefinations with a wider range of aldehydes than previously reported in the literature. In fact these are the first



Scheme 3. *Reagents and conditions*: (a) R-CHO, $MeReO_3$, $P(4\text{-Cl-Ph})_3$, DCM, rt, 18 h.

Table 2. Metal-catalysed olefination of **1** with aldehydes

R[a]	Product	*T* (°C)	Yield[d] (%)	*E*:*Z* ratio
4-Nitrophenyl	**3**	25	40	>10:1
3-Cyanophenyl	**8**	25	30	~10:1
2-Methylphenyl[b]	**9**	50	20	~10:1
4-Methoxyphenyl[c]	**10**	50	40	6:1
3-Thienyl	**11**	25	15	>10:1
5-Nitrothien-2-yl	**12**	25	44	>10:1
5-Nitrofuran-2-yl	**13**	25	52	7:1
3-Benzothienyl	**14**	25	22	>10:1
3-Quinolyl	**15**	25	25	>10:1
1-(4-Chlorobenzyl)-pyrazol-3-yl	**16**	25	46	8:1
1-Buten-4-yl	**17**	25	20	>10:1
1-Phenylethyl	**18**	25	15	>10:1
1-Phenylpropyl	**19**	25	22	~10:1

[a] Reactions carried out according to procedure A.[9]

[b] Chloroform used as solvent.

[c] THF used as solvent.

[d] Isolated yields of analytically pure compounds.[10]

reports of the olefination of any diazo compound with heterocyclic aldehydes. The reaction allows a rapid access to 3-substituted-piperidin-2-ones under very mild conditions which tolerate a wide range of functional groups. Although the yields are moderate this procedure compares well with the overall yields of published approaches to 3-alkylated-piperidin-2-ones. These approaches are generally multistep and use harsher reaction conditions.[11–13] These modified catalytic systems are being applied to the olefination of ethyl diazoacetate and results from this work will be reported shortly.

Acknowledgements

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9. **General Procedure A:** To a stirred solution of methyl trioxorhenium (0.25 mmol), tris(*p*-chlorophenyl)-phosphine (or diphenyl-2-pyridyl phosphine), (2.5 mmol) and the aldehyde (2.5 mmol) in DCM (10 ml) was added a solution of 3-diazopiperidin-2-one (2.5 mmol) in DCM (5 ml) dropwise at room temperature under an atmosphere of N_2. The reaction mixture was stirred at 25°C for 18 h. The resulting solution was concentrated in vacuo and purified by silica gel chromatography eluted with ethyl acetate.
10. All compounds decribed have been fully characterised by IR, MS and NMR spectroscopy, elemental analysis or accurate mass MS and by mp. For example: **3-[(2-Oxopiperidin-3-ylidene)methyl]benzonitrile 8.** *E-isomer*: Mp 189–191°C; IR (nujol) ν_{max} (cm^{-1}) 3168, 2229, 1660, 1612; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.76 (1H, s), 7.70–7.40 (4H, m), 6.18 (1H, bs), 3.46 (2H, dt, $J=5.7$, 2.7 Hz), 2.77 (2H, dt $J=6.0$, 3.0 Hz), 1.90 (2H, quintet, $J=6.0$ Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 165.80, 137.05, 134.00, 133.1, 132.7, 131.9, 131.3, 129.3, 118.7, 112.7, 42.1, 26.2, 22.9; APCI–MS *m*/*z* 213 [M+H]$^+$. Anal. found: C 73.48, H 5.63, N 13.15%; calcd for $C_{13}H_{12}N_2O$: C 73.56, H 5.66, N 13.20%. **3-[(5-nitro-2-furyl)methylene]piperidin-2-one 13.** *E-isomer:* Mp 212–214°C; IR (nujol) ν_{max} (cm^{-1}) 3125, 2687, 1670, 1617, 1467, 1341, 1214, 970, 808; ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.06 (1H, bs), 7.79 (1H, d, $J=4$ Hz), 7.36 (1H, t, $J=2$ Hz), 7.13 (1H, d, $J=4.1$ Hz), 3.26 (2H, td, $J=6.1$, 2.7 Hz), 2.93 (2H, dt, $J=6.5$, 2.0 Hz), 1.82 (2H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 163.2, 154.1, 151.5, 135.7, 118.5, 116.8, 114.6, 40.7, 26.4, 22.1; HRMS calcd for $C_{10}H_{11}N_2O_4$: 223.0719 [M+H]$^+$, Found 223.0718 [M+H]$^+$. **3-(1-Benzothien-3-ylmethylene)piperidin-2-one 14.** *E-isomer*: Mp 229–230°C; IR (nujol) ν_{max} (cm^{-1}) 3167, 2988, 1665, 1607, 1478, 1408, 1066, 763; ^{1}H NMR (CDCl$_3$, 400MHz) δ 8.07 (1H, s), 7.95 (1H, dd, $J=7.2$, 1.3 Hz) 7.87 (1H, dd, $J=7.3$, 1.0 Hz), 7.47 (1H, s), 7.42 (2H, m), 6.27 (1H, bs), 3.46 (2H, m, $J=5.6$, 2.7 Hz), 2.87 (2H, m, $J=6.0$, 2.1 Hz), 1.92 (2H, m, $J=6.0$ Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 166.4, 139.3, 139.0, 131.4,

130.6, 127.2, 126.3, 124.9, 124.5, 122.6, 122.3, 42.0, 27.0, 22.9; HRMS calcd for $C_{14}H_{14}NOS$: 244.0796 $[M+H]^+$, Found 244.0804 $[M+H]^+$. Anal. found: C 69.07, H 5.45, N 6.10, S 13.13% calcd for $C_{14}H_{13}NOS$: C 69.11, H 5.39, N 5.76, S 13.18%. **3-(2-Phenylethylidene)piperidin-2-one 18.** *E-isomer*: A foam; IR (nujol) ν_{max} (cm^{-1}) 3167, 2934, 1670, 1619, 1483, 1411, 1338, 1081, 752, 696; ^1H NMR ($CDCl_3$, 300MHz) δ 7.33–7.16 (5H, m), 7.05 (1H, t, $J=7.7$ Hz), 5.97 (1H, bs), 3.49 (2H, d, $J=7.7$) 3.37 (2H, m), 2.60 (2H, t, $J=6.0$ Hz), 1.90 (2H, m, $J=6.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 139.6, 134.9, 133.4, 128.5, 128.4, 126.1, 40.9, 33.0, 24.2, 22.7; HRMS calcd for $C_{13}H_{16}NO$: 202.1232 $[M+H]^+$, Found 202.1226 $[M+H]^+$. **3-(3-Phenylpropylidene)piperidin-2-one 19.** *E-isomer:* 118–120°C; IR (nujol) ν_{max} (cm^{-1}) 3177, 2926, 1670, 1622, 1484, 1335, 745, 696; ^1H NMR ($CDCl_3$, 300MHz) δ 7.33–7.14 (5H, m), 6.91 (1H, dt, $J=6.0$, 3.0 Hz), 6.01 (1H, bs), 3.36–3.28 (2H, m), 2.76 (2H, t, $J=7.9$ Hz), 2.45 (2H, q, $J=7.6$ Hz), 2.35 (2H, t, $J=6.0$ Hz), 1.75 (2H, m, $J=6.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 141.3, 135.4, 130.9, 128.4, 128.2, 125.8, 40.81, 34.1, 28.7, 24.1, 22.5; HRMS calcd for $C_{14}H_{18}NO$: 216.1388 $[M+H]^+$, Found 216.1367 $[M+H]^+$.

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