Pergamon

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Tetrahedron Letters 44 (2003) 8153–8156

TETRAHEDRON LETTERS

Intermediates in the synthesis of nitrogen heterocycles: addition of acylated camphorsultams to nitroalkenes

Joanna E. Clare,[a] Christine L. Willis,[a,*] Josephine Yuen,[a] Kenneth W. M. Lawrie,[b] Jonathan P. H. Charmant[c] and Anob Kantacha[c]

[a]*School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK*
[b]*GlaxoSmithKline, Gunnel's Wood Road, Stevenage, Herts, SG1 2NY, UK*
[c]*Structural Chemistry Laboratory, School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK*

Received 6 August 2003; accepted 1 September 2003

Abstract—Reaction of acylated camphorsultam **7** with nitroalkenes in the presence of $TiCl_4$ and Et_3N gave addition products in good yields (>70%) and with excellent stereocontrol. Addition of propionylated camphorsultam **15** to nitrostyrene gave the addition product **16** in which two new asymmetric centres were created, the stereochemical outcome of the reaction was confirmed by X-ray cystallography.

Nitro containing compounds are particularly versatile intermediates in organic synthesis. They facilitate carbon–carbon bond forming reactions and the nitro group may be readily transformed into a wide range of functionalities including reduction to amines and via a Nef reaction to carbonyl compounds.[1] In a previous paper we have shown that reaction of nitromethane with (1*S*,2*R*)-*N*-[(*E*)-crotonyl]bornane-10,2-sultam **1** in the presence of DBU in THF and DMPU gave a 3:1 mixture of diastereomers **2** and **3** in 90% yield. The major product **2** was purified by crystallisation from methanol (Scheme 1) and the structure confirmed by X-ray crystallography.[2] Hydrolytic cleavage of the auxiliary gave (*S*)-3-methyl-4-nitrobutanoic acid **4**, a valuable building block for the synthesis of *cis*- and *trans*-3-hydroxy-5-methylpiperidin-2-ones **5** and **6** in good yields using biotransformations to create the asymmetric centre at C-3 with complete stereocontrol. In order to improve this approach to the synthesis of hydroxypiperidinones, a more efficient method for the preparation of **4** is required.

An attractive option was to consider a different disconnection of **2** in a retro-Michael mode giving the acylated sultam **7** and (*E*)-1-nitroprop-1-ene (Scheme 1). Nitroalkenes are among the most powerful Michael acceptors and indeed such reactions have been carried out using acylated chiral auxiliaries.[3] The nearest literature precedent we found for the proposed reaction of **7** with (*E*)-nitropropene was by Brenner and Seebach being addition of acyloxazolidinone **8** to nitropropene in the presence of titanium tetrachloride and diisopropylethylamine giving a 9:1 mixture of diastereomers **9a** and **10a** from which the major product **9a** was isolated in 36% yield (Scheme 2).[4] Although the yield was disappointing, the diastereoselectivity was a significant improvement on the 3:1 mixture of **2** and **3** which we had obtained from the conjugate addition of nitromethane to the chiral crotonate **1**,[2] and so we were encouraged to proceed.

We have shown previously that aldol products are formed in good yield by reaction of acylated sultam **7** with a variety of aldehydes mediated by titanium tetrachloride and an amine base (e.g. diisopropylethylamine).[5] Thus, we anticipated that reaction of **7** with nitropropene under similar conditions would give a good yield of **2**/**3**. We now report the results of our investigations on the reactions of (*E*)-nitroalkenes with camphorsultams **7** and **15**.

Results and Discussion

(*E*)-Nitropropene[6] and acylcamphorsultam **7** were treated with $TiCl_4$ and Et_3N in CH_2Cl_2 at −78°C. The reaction mixture was quenched with aqueous NH_4Cl at −78°C and following a standard extraction protocol a

* Corresponding author.

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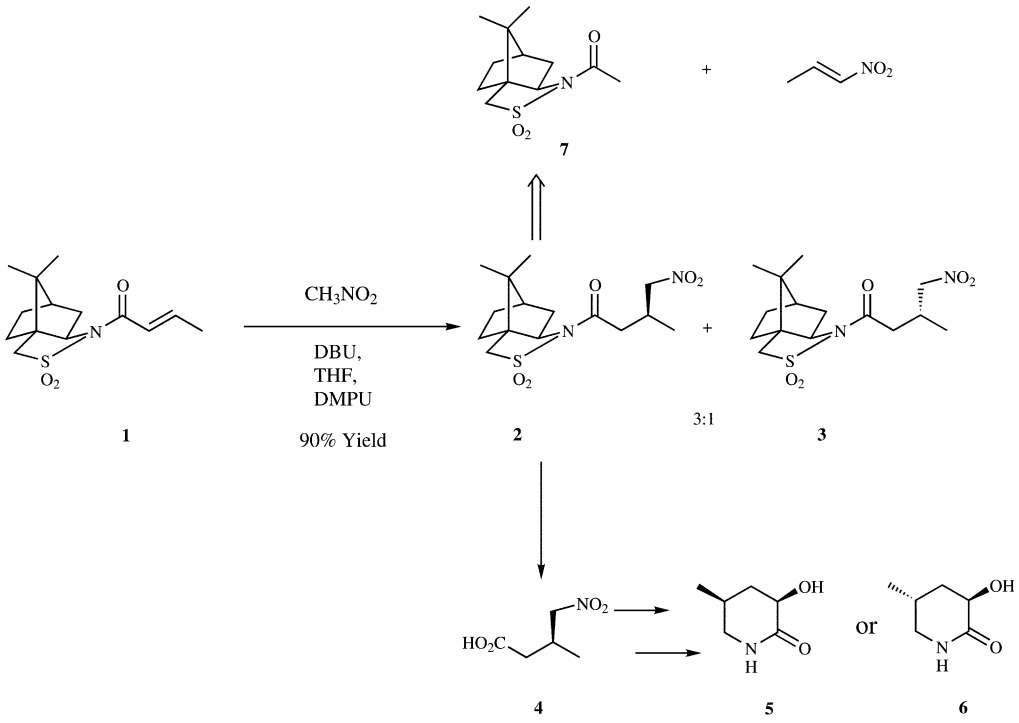
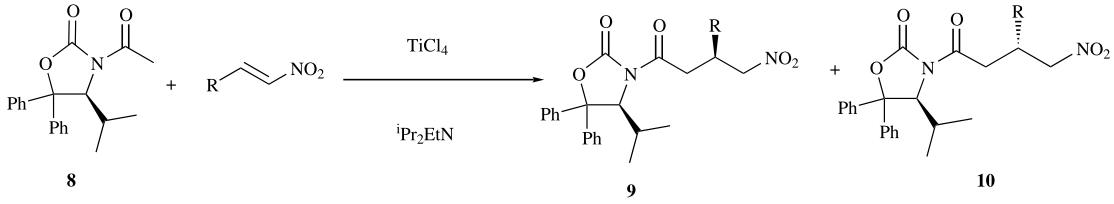
doi:10.1016/j.tetlet.2003.09.029



Scheme 1.

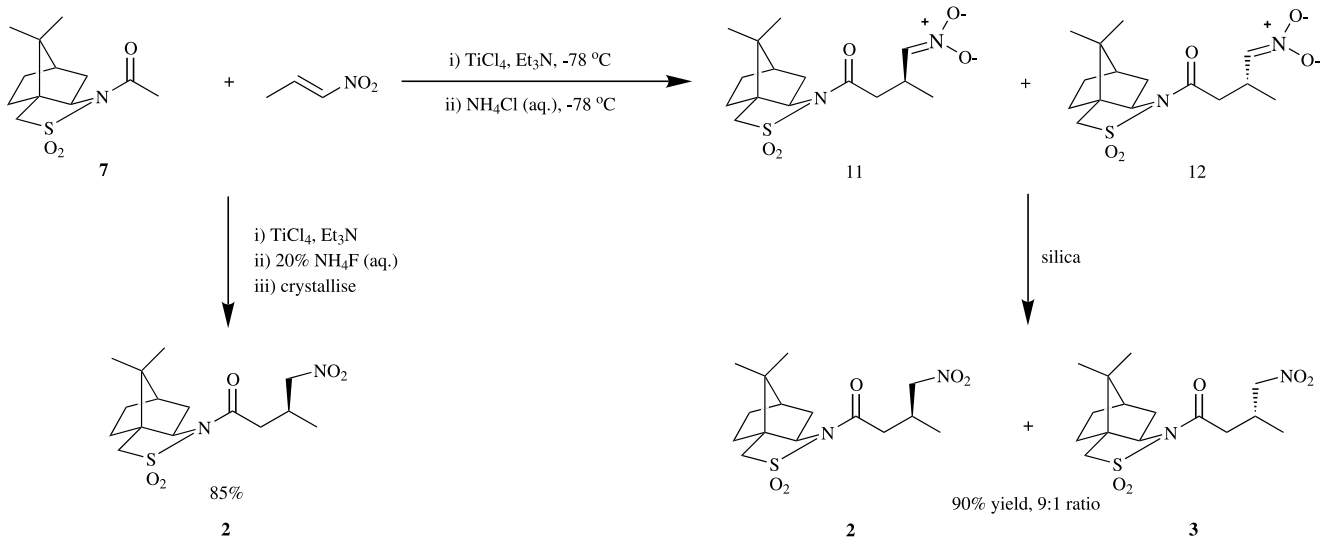


		ratio **9**:**10**
9a	R=Me, 36% yield;	9:1
9b	R=Ph, 72% yield;	96:4
9c	R=^{i}Pr, 53% yield;	88:12

Scheme 2.

9:1 mixture of products was apparent by ^{1}H and ^{13}C NMR spectroscopy (Scheme 3).[7] The ^{1}H NMR spectrum revealed the presence of a doublet (J 7.5 Hz) at δ 6.22, characteristic of the nitronate intermediate **11**. A minor amount (ca 10%) of the 3′*R*-nitronate **12** was apparent in the spectrum and only a trace of the nitro derivative **2** in which the 4′-protons resonate in the region δ 4.0–4.5 ppm. The crude product was purified by flash chromatography giving **2** and **3** in a pleasing 90% yield and the major diastereomer was further purified by crystallisation.[8]

From this result it is apparent that reaction of nitropropene with acylated sultam **7** gave a significantly higher yield of addition product **2** (Scheme 3) compared with the analogous reaction with acylated oxazolidinone **8** although the stereoselectivity in each case was similar (Scheme 2). However, as well as changing the auxiliary, a further difference between the two experiments was the work-up procedure. Brenner and Seebach[4] reported that, following the reaction, the organic phase containing the crude product was washed sequentially with acid, base and then again with acid. Thus we repeated the reaction of acylated sultam **7** with nitropropene and worked-up the reaction under these conditions. No nitronate **11** was observed in the ^{1}H NMR spectrum of the crude material but, in this case, the addition products **2** and **3** were isolated in only 67% yield following flash chromatography compared with a 90% yield on working up the reaction mixture simply with aqueous NH_4Cl prior to flash chromatography. For further comparison, we treated acyloxazolidinone **8**



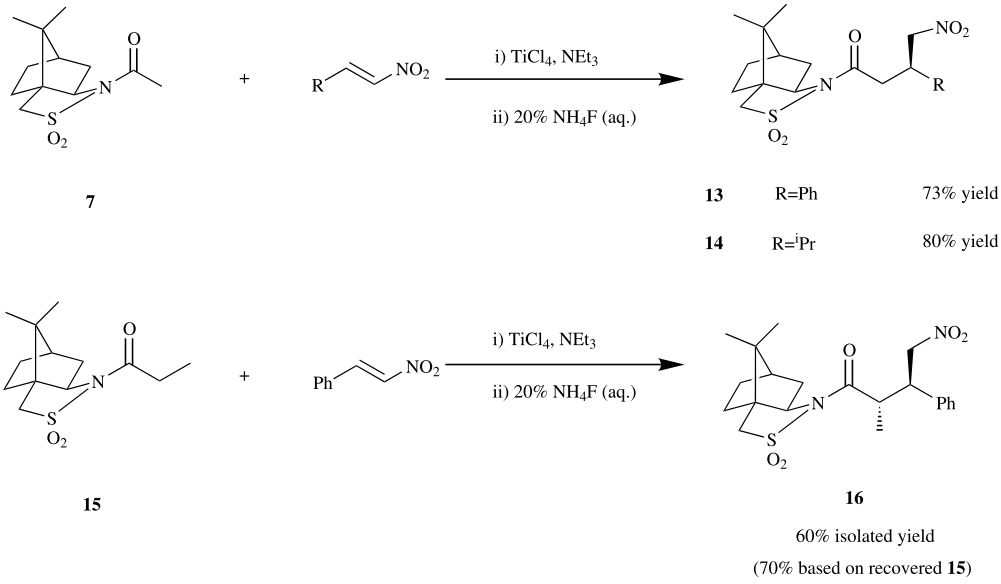
7 11 12 2 2 3

Scheme 3.

and nitropropene with $TiCl_4$ and iPr_2EtN and worked up the reaction either by quenching with aqueous NH_4Cl or using the more elaborate acid/base/acid wash giving **9a** in 52% and 33% yield respectively after flash chromatography. Thus it is apparent that the work-up procedure does indeed have a significant effect on the yield of isolated addition products. In the examples reported above, higher yields of products were obtained by a simple work-up with aqueous NH_4Cl followed by purification by flash chromatography on silica.

Since **2** is crystalline, ideally we required a work-up procedure for the reaction of acylated sultam **7** and nitropropene with $TiCl_4$ and Et_3N which avoided the necessity of using silica to breakdown the nitronate **11**. This was achieved by quenching the reaction mixture with aqueous ammonium fluoride[4] at −78°C and, following crystallisation from methanol, the analytically pure product **2** was isolated in 85% yield.

If these reactions are to be valuable in the stereocontrolled synthesis of substituted piperidin-2-ones other than the *cis*- and *trans*-3-hydroxy-5-methylpiperidin-2-ones **5** and **6**, then the diastereoselective addition of acylated sultam **7** to a range of nitroalkenes must be achieved. Treatment of **7** with nitrostyrene under the standard conditions gave the diastereomer **13** as the sole product in 73% yield whilst with (*E*)-1-nitro-3-methylprop-1-ene the isopropyl derivative **14** was isolated in 80% yield, again as a single diastereomer (Scheme 4). In each case, the reactions were worked up using aqueous ammonium fluoride. Finally we found that reaction of propionyl sultam **15** and nitrostyrene with $TiCl_4$ and Et_3N gave **16** with the creation of 2 new



7

13 R=Ph 73% yield

14 R=^{i}Pr 80% yield

15 16

60% isolated yield

(70% based on recovered **15**)

Scheme 4.

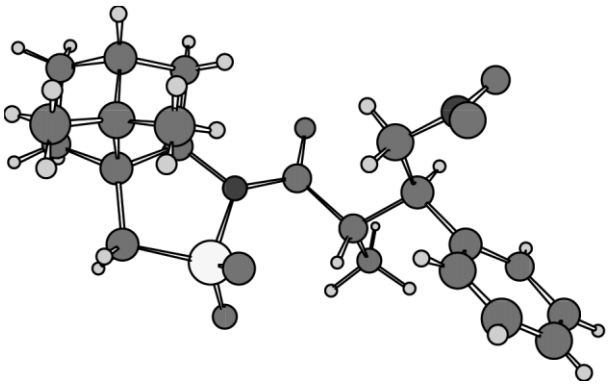


Figure 1. X-Ray structure of **16**.

asymmetric centres in >98% de and 70% yield (based upon recovered starting material, 60% isolated yield).

The product **16** was crystallised from toluene and X-ray crystallography confirmed the stereochemical outcome of the reaction (Fig. 1).[9]

In conclusion, we have shown that the titanium tetrachloride promoted reaction of acylated camphor sultams with nitroalkenes in the presence of base gives good yields of addition products and the creation of new asymmetric centres with excellent stereocontrol. We have also demonstrated that the work-up procedure has a significant effect on the yields of the isolated products.

Acknowledgements

We are grateful to the EPSRC and GSK for funding to J.E.C.

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6. Nitroalcohols were prepared by the method of Lucet, D.; Sabelle, S.; Kostelitz, O.; LeGal, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583–2591; nitroalkenes were prepared according to the method of Denmark, S. E.; Schuter, E. *J. Org. Chem.* **1995**, *60*, 1013–1019.
7. General procedure for conjugate addition: sultam (1 equiv.) in CH_2Cl_2 (0.3 M) was cooled to −78°C under N_2. $TiCl_4$ (1.0M in CH_2Cl_2, 2 equiv.) was added and the yellow solution stirred for 10 minutes. Triethylamine (1.2 equiv.) was added dropwise to give a dark red suspension and the mixture stirred for 30 minutes. The nitroalkene (2 equiv.) was taken up in CH_2Cl_2 (3 M) then added dropwise to the reaction mixture. After stirring for 4.5 hours at −78°C the reaction was quenched and worked up by one of the following methods.
   Workup A: The reaction mixture was quenched at −78°C with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic fractions were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to yield the crude nitronate. Purification by column chromatography eluting with increasing percentage of EtOAc in light petroleum gave the addition product.
   Workup B: The reaction mixture was quenched at −78°C with aqueous 20% NH_4F. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to yield the crude product. Recrystallisation from methanol gave the addition product.
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