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Sequential Nitromethane Conjugate Addition/Elimination–Pd-Catalyzed Allylation of β-Trifloxy Acrylates. Application to Carbapenem Synthesis

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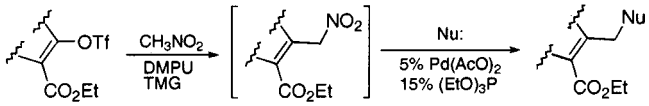
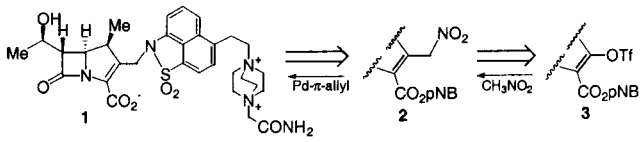
ABSTRACT



Sequential reactions of nitromethane via conjugate addition–elimination to β-trifloxy acrylates followed by Pd-catalyzed substitution of the resulting allyl nitro compounds with nucleophiles afforded homologation products at the β-position. 2-Naphthosultammethyl carbapenem, an anti-MRS carbapenem intermediate, was prepared in one pot from the corresponding 2-trifloxy compound. The scope and limitation of the one-pot method were investigated using several cyclic unsaturated esters and nucleophiles.

The use of sequential reactions to improve synthetic efficiency has been well-recognized.[1−3] In connection with our work on the anti-MRS carbapenem **1**,[4,5] we were interested in combining nitromethane conjugate addition and Pd-catalyzed allylation reactions for functionalization at the C-2 position (Scheme 1). It is well known that nitroalkanes can

Scheme 1



display either electrophilic or nucleophilic behavior at the α-position.[6,7] To take advantage of this "chameleon" property, we planned to add nitromethane to the 2-trifloxy compound **3** and use the resulting allyl nitro compound (**2**) for a Pd-catalyzed allylic substitution with the naphthosultam. Herein we report a one-pot version of this process and preliminary results on the scope and limitations of the overall sequence.

Previously, Yoshioka et al. prepared the acid-labile 2-(nitromethyl)carbapenems from 2-(sulfinyl)carbapenem and nitromethane in moderate yields.[8] We applied this method to carbapenem sulfoxide **4**, which was prepared from triflate **6** (1. EtSH/^{i}Pr$_2$NEt/CH$_3$CN, 75%; 2. MCPBA/CH$_2$Cl$_2$, 90%).[5,9] Initial studies (CH$_3$NO$_2$/5 equiv of TMG (tetramethylguanidine)/−15 °C/3.5 h) did produce 2-nitromethyl-*O*-TBS-β-

(1) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
(2) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.
(3) Parson, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.
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(6) Boyd, G. V. In *Supplement F2: The chemistry of amino, nitroso, and related groups*; Patai, S., Ed.; Wiley: New York, 1996.
(7) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423.
(8) Yoshioka, T.; Yamamoto, K.; Shimauchi, Y.; Fukagawa, Y.; Ishikura, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1513.
(9) Yasuda, N.; Huffman, M. A.; Ho, G.-J.; Xavier, L. C.; Yang, C.; Emerson, K. M.; Tsay, F.-R.; Li, Y.; Kress, M. H.; Rieger, D. L.; Karady, S.; Sohar, P.; Abramson, N. L.; DeCamp, A. E.; Mathre, D. J.; Douglas, A. W.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 5438.

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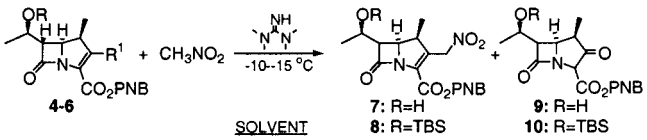
methylcarbapenem **8** in low yield (10% yield after a quick purification through a short silica column). The structure of **8** was confirmed by ^{1}H and ^{13}C NMR ($CDCl_3$) [AB quartet at δ 5.97 and 5.10 for the nitromethylene protons] and by CI mass spectra (NH_3) with observed molecular ions at 520 (MH^+) and 537 ($M + NH_4^+$).[10]

In an effort to improve the yield, we studied two other substrates in the nitromethane addition reaction. Starting from enol phosphate **5**, the desired product **7** was again formed in low yield with keto−ester **9** as the major product as judged by LC and NMR of the reaction mixture after workup (Scheme 2). Further attempts were carried out in the presence

Scheme 2



	SOLVENT	8		10
4: R=TBS, R^1=SOEt	CH_3NO_2	1	:	-
5: R=H, R^1=OPO(OPh)$_2$	CH_3NO_2	1	:	5
"	DMPU:CH_3NO_2 1:1	1	:	3
"	HMPA:CH_3NO_2 1:1	1	:	2.8
6: R=TBS, R^1=OTf	DMPU:CH_3NO_2 1:1	5-10	:	1

of cosolvents, DMPU or HMPA.[11] In all cases, keto−ester **9**, presumably arising from attack on the phosphorus, is the major reaction product and the desired product **7** was the minor product, formed in respective ratios of 3−5:1.[12]

Significant improvement was obtained by starting with triflate **6** and DMPU as the cosolvent with nitromethane. After workup, the unstable oily product was partially purified by being filtered through a silica pad. The estimated yield of **8** was 60−70% based on LC and low-temperature NMR analysis. The ratio of nitromethyl product **8** to keto−ester **10** ranged from 5 to 10:1[12] depending on the amounts of base and nitromethane used.

To rationalize the observed reversal of chemoselectivity between the two substrates and gain insight into the electronic nature of these reacting species, we have performed molecular orbital calculations on model compounds **11**, **12**, and **13**. Frontier orbitals for aci-nitromethane and two carbapenems were generated using PC SPARTAN program[13] at the 3-21G* level (Figure 1). We found that the aci-nitromethane HOMO corresponded well with the LUMO of the phosphorus atom in **13** but did not match the LUMO at C2. This is consistent with the principal attack being on the phosphorus of the phosphate. In contrast, the LUMO at C2 of triflate **12** is better matched with the HOMO of aci-nitromethane than the sulfur atom's, and therefore the preferred attack is on the C-2 carbon rather than the sulfur of the triflate.

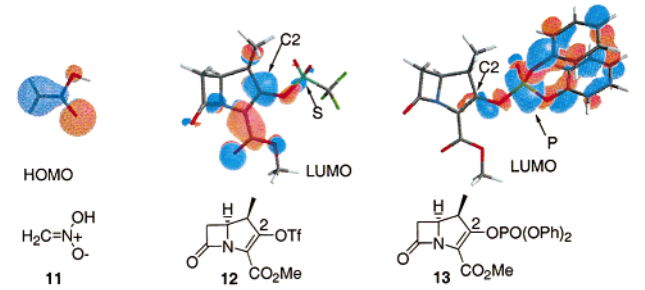
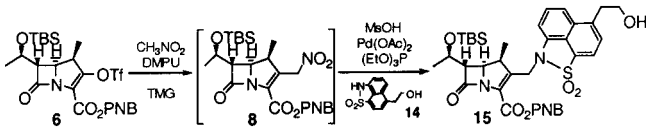


Figure 1. Frontier orbitals.

With **8** in hand, we next examined the Pd-catalyzed allylic coupling with hydroxyethylnaphthosultam **14**.[14] Initial studies with isolated nitromethyl compound **8** under biphasic conditions (toluene/THF, aqueous $NaHCO_3$, $Pd(OAc)_2$, $(EtO)_3P$) produced low yields of desired product **15**, along with substantial quantities of *p*-nitrobenzyl alcohol. Given the instability of the isolated nitromethyl intermediate, our attention was then focused on developing a through process from the enol triflate. Thus, treatment of enol triflate **6** in 1:1 DMPU/CH_3NO_2 at −20 °C with 6 equiv of TMG followed by aging for 1−2 h afforded complete consumption of starting material (Scheme 3). Subsequent partial neutral-

Scheme 3



ization with MsOH (4 equiv), addition of naphthosultam **14** (1 equiv), $Pd(OAc)_2$ (5%), and $(EtO)_3P$ (15%) and aging at rt for 1−2 h led to complete consumption of **8** to afford the desired product **15**. The overall assay yield of **15** is 34% for the two steps. Workup with pH 7 buffer provided a 97% recovery of product with good rejection of unreacted **14**. Thus, a sequential nitromethane conjugate addition reaction to triflate **6** and the Pd(0)-catalyzed coupling of the resulting nitromethyl **8** with hydroxyethylnaphthosultam **14** was demonstrated.

(10) **8**: ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 5.97 (AB d, J = 14.9 Hz, 1H), 5.43 (AB d, J = 13.9 Hz, 1H), 5.26 (AB d, J = 13.9 Hz, 1H), 5.10 (AB d, J = 14.9 Hz, 1H), 4.37 (dd, J = 10.7, 3.4 Hz, 1H), 4.26 (dd, J = 6.0, 5.2 Hz, 1H), 3.35 (dd, J = 4.8, 3.4 Hz, 1H), 3.29 (m, 1H), 1.21 (d, J = 6.0 Hz, 3H), 1.18 (d, J = 8.0 Hz, 3 H), 0.84 (s, 9H), 0.07 (s, 3H), 0.06, (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.6 (CON), 160.2 (CO_2), 147.7, 142.1, 136.7, 132.3, 128.1 (PNB), 123.9 (PNB), 70.7 (CH_2NO_2), 65.9 (CH_2(PNB)), 65.3 (C8), 61.2 (C6), 55.5 (C5), 40.7 (C1), 25.6 (tBu), 22.1 (C9), 15.1 (C1a), −4.3 (SiMe), −5.1 (SiMe); MS (CI), 520 (MH^+) and 537 ($M + NH_4^+$).

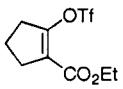
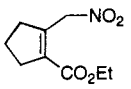
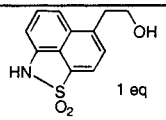
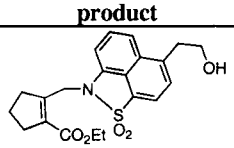
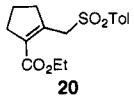
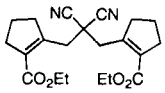
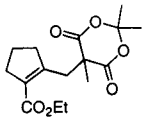
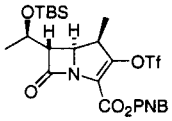
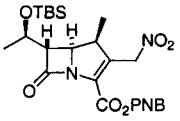
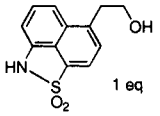
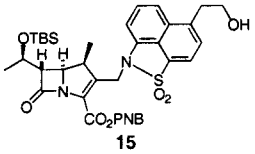
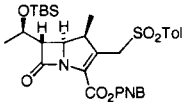
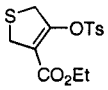
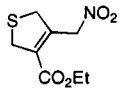
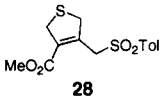
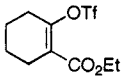
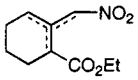
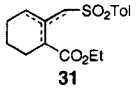
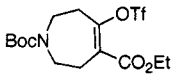
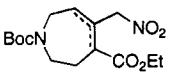
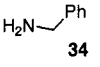
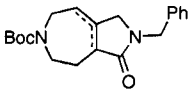
(11) Previous studies indicated that HMPA or DMPU can stabilize the carbapenem: see ref 5.

(12) Based on LC area % at 260 nm.

(13) Available from Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612.

(14) Humphrey, G. R.; Miller, R. A.; Lieberman, D. R. W.O. Patent 9851677, 1998.

Table 1. One-Pot Nitromethane Addition−Elimination and Pd-Cataylzed Allylation of β-Triflate Acrylate Derivatives[a]

entry	starting material	nitro product	yield[b]	nucleophiles	allylated product	overall yield[b]
1	 **16**	 **17**	90-95%	 1 eq **14**	 **18**	57%
2	"	"	"	$NaSO_2Tol$ 2 eq **19**	 **20**	87%
3	"	"	"	 1 eq **21**	 **22**	73%
4	"	"	"	 2 eq **23**	 **24**	74%
5	 **6**	 **8**	60-70%	 1 eq **14**	 **15**	34%
6	"	"	"	$NaSO_2Tol$ 2 eq **19**	 **25**	55%
7	 **26**	 **27**	40%	$NaSO_2Tol$ 1 eq **19**	 **28**	26%
8	 **29**	 **30**	45%	$NaSO_2Tol$ 1.5 eq **19**	 **31**	35%
9	 **32**	 **33**	80-85%	 2 eq **34**	 **35**	71%[c]

[a]Reactions were carried out with 1-2 mmol of the enol triflate and 5-6 eq of TMG in 0.3 M of 1:1 CH_3NO_2:DMPU at 0-20 °C for 1-20 h. Then, added 3-4 eq MsOH, 1-2 eq of nucleophile, 5% $Pd(OAc)_2$ and 15% $(EtO)_3P$ and aged at rt for 1-2 h. [b] LC Assay yield. [c]The allylation was performed in DMPU using isolated crude **33**.

A brief optimization study of the nitromethane addition reaction provided the following observations: (1) Base basicity had a huge effect. Triethylamine is not effective at all, with either DBU or TMG being preferable. (2) Low temperatures gave better results (−20 vs 0 °C). (3) DMPU and NMP were better cosolvents than toluene or THF. (4) High concentrations of base and nitromethane gave better yields.

The scope and limitation of this one-pot sequential reaction was briefly investigated using several enol triflates and nucleophiles. The allyl nitro products could be isolated by MTBE or EtOAc extraction of the reaction mixture followed by aqueous washes. In most cases it is not necessary to isolate the nitro product and the crude mixture could be taken into the Pd-catalyzed allylation step after neutralization. Starting from ethyl 2-(trifluoromethylsulfonyloxy)-1-cyclopentene-1-carboxylate (**16**), the assay yield of nitromethyl intermediate **17** is 90−95% (DMPU:CH_3NO_2 1:1, 0.3 M, 0−22 °C, 4 h). Without DMPU, the yield of **17** is lowered to ~70%. Four nucleophiles, hydroxyethylnaphthosultam **14**, sodium tolylsulfinate (**19**), malonitrile (**21**), and methyl Meldrum's acid (**23**) all added smoothly to **17** in the Pd-catalyzed allylation, except for **21** which afforded only the bis-alkylation product, even when excess **21** was used. The homologated products were obtained in 58−87% overall yield for the two steps (Table 1, entries 1−4). Tosylate **26** gave a lower yield of the nitro product (entry 7). The six- and seven-membered triflates (**29** and **32**) gave a mixture of olefin isomers (entries 8 and 9).

Acknowledgment. We thank Ms. L. M. DiMichel and Mr. R. A. Reamer for their help with the NMR studies.

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