Conversion of *N*-Acyllactams into *α*-Alkylated Cyclic Enamides *via* Vinyl Triflates

Kazunori Tsushima, Tetsuya Hirade, Hirohiko Hasegawa, and Akio Murai*
Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060

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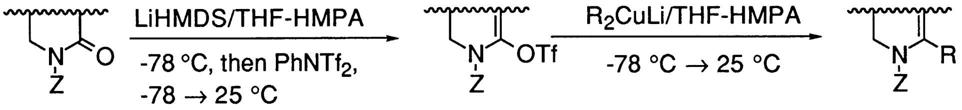
N-Acylated six- or seven-membered lactams were converted effectively into various α-alkylated cyclic enamides *via* their corresponding vinyl triflates.

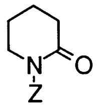
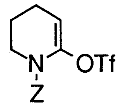
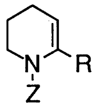
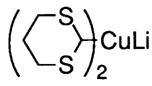
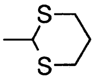
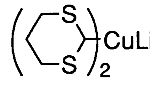
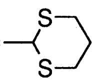
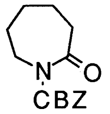
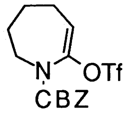
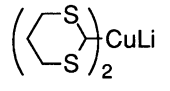
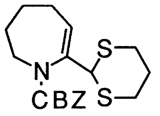
Recently, we have reported the transformation of medium sized lactones into α-alkylated cyclic ethers *via* vinyl triflates[1,2] and its application to the total syntheses of (+)-lauthisan[2] and (+)-laurencin,[3] and construction of the tetracyclic framework in hemibrevetoxin-B.[4] We have further studied to develop the reaction into the lactam series. Very recently, Comins and co-worker have published conversion of *N*-acyllactams to the corresponding vinyl triflates.[5] Their results have prompted us to report our preliminary approach to the similar reactions using *N*-acyllactams, which is described herein.

The *N*-acylation of δ-valerolactam or ε-carprolactam was performed feasibly upon treatment with NaH in THF and then with PhCOCl (-78 °C → 25 °C, 12 h), Boc_2O (0 °C → 15 °C, 12 h), or with $PhCH_2OCOCl$ (0 °C, 15 min and 25 °C, 1 h) in 55-90% yield (Table 1). To each *N*-acyllactam was added a solution of LiHMDS in THF at -78 °C for 35 min and the mixture was stirred for 70 min. HMPA (2 eq) was then added and the mixture was stirred at -78 °C for 15 min. A solution of $PhNTf_2$ in THF was added at the temperature and the mixture was allowed to stand at -78 °C to room temperature during the period of 15 h to give the corresponding vinyl triflates (**5a**, **5d**, and **5h**) in 67-94% yield.[6,7] In contrast to the case of lactone vinyl triflates, these products are rather stable on standing in air. The vinyl triflates obtained thus were allowed to react with various lithium dialkylcuprates to afford the corresponding α-alkylated cyclic enamides (**6a**-**h**) in good yields, respectively, as summarized in Table 1. The data reveal that (i) six- or seven-membered lactams (**5a**, **5d**, and **5h**) were able to be converted

Table 1. Conversion of *N*-acyllactams to α-alkylated cyclic enamides *via* vinyl triflates



1 2 3

entry	*N*-Acyllactams	Yield (%)	Vinyl triflates	Yield (%)	R_2CuLi	α-Alkylated Cyclic Enamides	Yield (%)
							
1	**4a** Z=COPh	61	**5a** Z=COPh	94	t-Bu_2CuLi	**6a** Z=COPh, R=t-Bu	69
2					Ph_2CuLi	**6b** Z=COPh, R=Ph	69
3						**6c** Z=COPh, R= 	96
4	**4d** Z=BOC	90	**5d** Z=BOC	89	Me_2CuLi	**6d** Z=BOC, R=CH_3	76
5					Bu_2CuLi	**6e** Z=BOC, R=Bu	73
6					Ph_2CuLi	**6f** Z=BOC, R=Ph	38
7						**6g** Z=BOC, R= 	71
8	 **4h**	55	 **5h**	67		 **6h**	85

smoothly to the corresponding alkylated cyclic enamides, although transformation of five-membered lactam didn't proceed so well;[8] (ii) in the case of **5a**, rather bulky alkyl groups are necessitated as the nucleophiles, because small alkyl groups attack the carbonyl part in the *N*-benzoyl group to afford alkylphenyl ketone;[9] (iii) the vinyl triflates with bulky acyl groups (**5d** or **5h**) are particularly efficient for alkylation with small alkylating groups such as methyl (entry 4) or butyl groups (entry 5). The typical alkylation reaction is as follows: To a solution of Me_2CuLi (1.5 mmol) in THF and HMPA (1.5 mmol), which was freshly prepared by addition of MeLi (3 mmol) in ether to the suspension of CuI (1.5 mmol) at -20 °C for 30 min, was added a solution of **5d** (0.3 mmol) in THF at -78 °C, and the mixture was stirred at -78 °C to 25 °C for 17 h and then diluted with hexane, followed by filtration through Celite. The filtrate was concentrated *in vacuo* to dryness and the residue was purified by short SiO_2 column chromatography (hexane-EtOAc 10:1) to yield **6d**[10] (0.23 mmol) as a colorless oil.

The results of these experiments seem to be valuable for the synthesis of various pharmaceuticals having substituted piperidine skeletons.[11]

References and Notes

1 K. Tsushima, K. Araki, and A. Murai, *Chem. Lett.*, **1989**, 1313.

2 K. Tsushima and A. Murai, *Chem. Lett.*, **1990**, 761.

3 K. Tsushima and A. Murai, *Tetrahedron Lett.*, **33** (30), 4345 (1992).

4 F. Feng and A. Murai, *Synlett*, in press.

5 C. J. Foti and D. L. Comins, *J. Org. Chem.*, **60**(9), 2656 (1995).

6 Comins et al. reported that enolate trapping of *N*-phenyloxycarbonyl six-membered lactam with $PhNTf_2$ was not as efficient (29% yield) comparing to *N*-(5-chloro-2-pyridyl)triflimide as their reagent.[5] Our results had no serious problems using $PhNTf_2$.

7 The yield in the vinyl triflate reaction of *N*-benzoyl-2-pyrrolidone amounted to only 30% (65% based on the recovered starting material).

8 When the vinyl triflate of *N*-benzoyl-2-pyrrolidone was treated with lithium bis(1,3-dithianyl)cuprate, the yield of the alkylated product amounted to only 16%.

9 When compound **5a** was treated with Bu_2CuLi in THF at -78 °C to 25 °C for 15 h, only 1-phenyl-1-pentanone was obtained as the sole product.

10 **6d**: IR (film), 2974, 2932, 1710, 1662, 1455, 1374, 1251, 1164, 1101, 1080, 1056, 876, and 768 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C), δ4.83~4.85 (1H, brs), 3.55~3.52 (2H, m), 2.04 (3H, s), 2.06~2.00 (2H, m), 1.77~1.71 (2H, m), and 1.48 (9H, s); EI-MS, m/z 197 (M^+), 183, 141, 140, 124, 96, 82, 68, 57, and 41; HR-EI-MS, Found 197.1413. Calcd for $C_{11}H_{19}O_2N$, 197.1416.

11 M. Rubiralta, E. Giralt, and A. Diez, Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives. In *Studies in Organic Chemistry*; Elsevier, New York (1991), Vol. 43, Chapter 1.