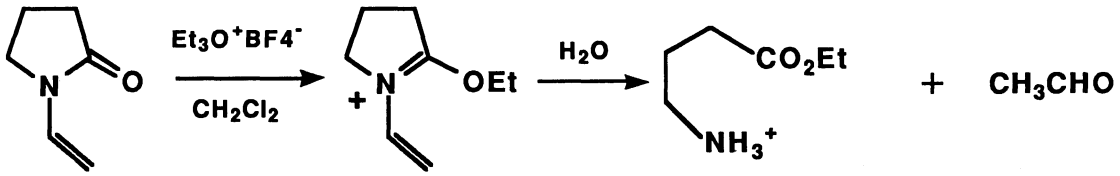
CHEMISTRY LETTERS, pp. 247-250, 1992.

A New Lactam Protecting Group

Michael B. SMITH,* Chung-Jen WANG, Paul F. KEUSENKOTHEN, Bruce T. DEMBOFSKY, Joseph G. FAY, Charles A. ZEZZA, Tae Woo KWON, JennLine SHEU, Young Chan SON, and Royce F. MENEZES
Department of Chemistry, U-60, Rm. 151, 215 Glenbrook Rd.,
University of Connecticut, Storrs, Connecticut, 06269-3060, U.S.A.

N-Alkenyl and *N*-alkoxymethyl lactams are impervious to many reagents and are useful protecting groups for lactams. Conversion to the corresponding 2-ethoxy iminium salt and hydrolysis in neutral water removes the protecting group. Mild basification regenerates the lactam.

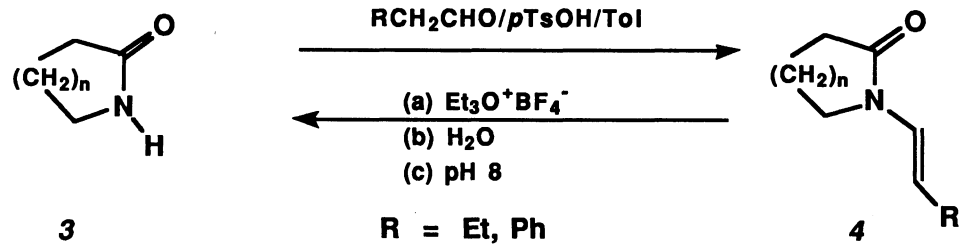
Lactams are an important structural component of many naturally occurring compounds and are useful intermediates in synthesis. Synthesis involving lactams usually requires protection of the N-H moiety. Greene describes amides as protecting groups for other functionality but does not discuss a single method for protection of lactams or amides.[1]



1 *2*

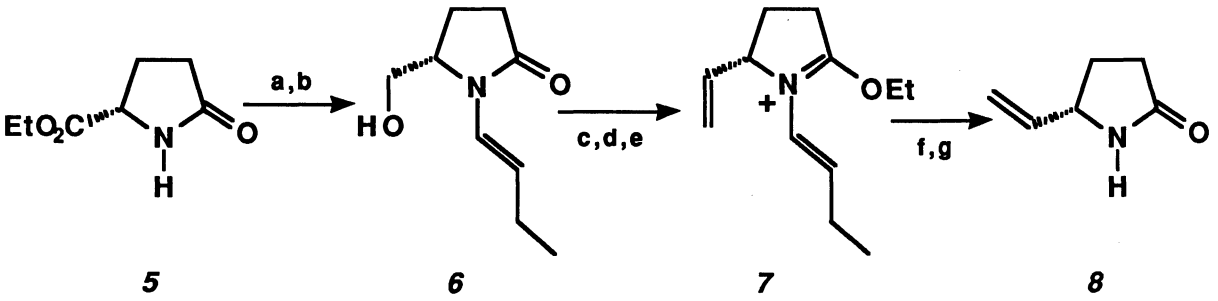
The literature contains several methods, however, and conversion to *t*-BOC[2] or Cbz[3] derivatives are common. *N*-Sulfonyl lactams are also known but are prepared indirectly by sulfonation of an ω-amino acid or ester followed by cyclization to the sulfonyl lactam,[4] or via Beckmann rearrangement of *O*-sulfonyl hydroxylamines.[5] We developed a method which allows more direct sulfonation of lactams via initial conversion to the *O*-methyl lactim followed by reaction with the appropriate sulfonyl halide in dichloromethane.[6] Other protecting groups have included *N*-benzyl,[2a,7] acetate,[8] trifluoroacetate,[9] trimethylsilyl[10] and *t*-butyldimethylsilyl.[11] Much of our recent work has focused on the use of *N*-alkenyl and *N*-alkoxymethyl lactams as pro-GABA derivatives[12] and in Diels-Alder reactions.[13,14] In this work, alkenyl or alkoxymethyl moieties protected the lactam from a variety of reaction conditions. *N*-Vinyl was reported to be a lactam protecting group by Brandänge and Lindblom, who converted *N*-vinyl-2-pyrrolidinone to 2-alkyl pyrrolines[15a] and also used it in condensation reactions with ethyl nicotinate.[15b] Spitzner used *N*-vinyl-2-pyrrolidinone in a synthesis of myosmine.[16] We expanded this idea and made it applicable to a wide range of lactams, based on our previous report that *N*-vinyl-2-pyrrolidinone reacted with triethyloxonium tetrafluoborate to produce 2-ethoxy-*N*-ethenyl-pyrrolidiniminium tetrafluoborate ***1*** in high yield.[12] Iminium salt ***1*** was hydrolyzed in neutral water to give ethyl 4-aminobutanoate ***2*** and acetaldehyde. Adjusting the pH of the solution to 8-9 (or often to neutrality) led to ring closure and isolation of 2-pyrrolidi-none. *N*-Alkenyl-2-pyrrolidinones were known prior to our work[17] and heating with 6N

HCl or concentrated sulfuric acid led to ring opening and formation of the amino acid (GABA).[18] We prepared alkenyl lactams by reacting an aldehyde and a lactam with *p*-toluenesulfonic acid in refluxing toluene or benzene.[13b] Treatment with Meerwein's salt and dissolution in water liberated the aldehyde under mild and neutral conditions. Our mild procedure generates amino ester intermediates, allowing basification and facile ring closure to the lactam.



3 R = Et, Ph *4*

In a variety of synthetic applications we found that alkenyl lactams are stable to oxidation (Moffatt, Swern, Jones', PDC and PCC), reduction ($NaBH_4$, $LiBH_4$, $LiAlH_4/SiO_2$)[19]), Wittig olefination (alkyl and allylic triphenylphosphonium ylids), halogenation (PPh_3 with bromine, CBr_4 and hexachloroacetone; thionyl chloride), S_N2 substitution (iodide, azide, cyanide), reactions with organometallics (Gilman and Lipshutz organocuprates, Grignards and organolithium reagents if a more highly reactive group such as aldehyde or ester is present), bases (NaH, anhydrous NaOH or KOH under phase transfer methods, lithium diisopropylamide and lithium hexamethyldisilazide) and thermolysis up to about 200 °C. Acid and base hydrolysis was very slow at pH ≈ 4-10. The alkenyl lactam decomposed with strong Lewis acids such as $AlCl_3$, but did not decompose with milder Lewis acids such as zinc chloride. Treatment with lithium aluminum hydrides reduces



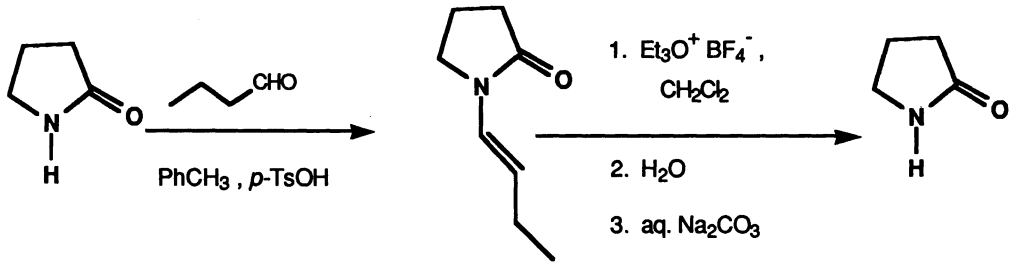
5 *6* *7* *8*

(a) $CH_3CH_2CH_2CHO$/*p*TsOH/Tol (b) $NaBH_4$ (c) DMSO/DCC
(d) Ph_3P^+-CH_3/*t*BuO$^-K^+$/THF (e) $EtO_3^+BF_4^-$ (f) H_2O (g) pH 8

the alkenyl lactam initially to an enamine, which is not isolated but is reduced further to an alkyl amine. Virtually any aldehyde can be used to protect the lactam, if it contains an enolizable hydrogen.[13b] We preferentially use butanal (to give the *N*-(1-butenyl) derivative), and phenylacetaldehyde (to give the *N*-2-phenyl-1-ethenyl derivative). These groups provide suitable protection, relatively clean NMR signals and aldehyde by-products which are conveniently removed. We therefore recommend butenyl and styryl as the protecting groups of choice. The generalized protection/deprotection sequence is illustrated for interconversion of ***3*** and ***4*** (R = Et, Ph).

A sequence that uses this protecting group is the conversion of ethyl pyroglutamate (***5***) to the *N*-butenyl derivative in 82% via reaction with butanal (*vide infra*). The carboethoxy group was reduced ($NaBH_4$, diglyme) to give the hydroxy-methyl derivative, ***6*** (80%). This was oxidized under Moffatt conditions (DCC, DMSO, heat) and the resulting

aldehyde was subjected to Wittig olefination conditions to give **7** in 59% overall yield. The butenyl protecting group was removed by treatment with triethyloxonium tetrafluoborate (to give the 2-methoxypyrrolidiniminium salt) and dissolution in aqueous sodium carbonate removed the butenyl group to give an amino ester, which cyclized to **8** under the reaction conditions.



9 **10**

A mixture of 100.6 mmol (8.563 g) of 2-pyrrolidinone and about 50 mg of *p*-toluenesulfonic acid were dissolved in 0.15 L of dry toluene, fitted with a Dean-Stark trap and reflux condenser and brought to vigorous reflux. A solution of 102.0 mmol (7.564 g) of butanal in toluene was injected into the refluxing solution and heated until the maximum amount of water was collected in the trap (about three hours). The solution was cooled to room temperature and washed once with 0.1 L of saturated sodium bicarbonate, followed by 0.1 L of water. The combined aqueous layers were extracted with 0.1 L of ether and the organic phases were dried ($MgSO_4$). The solution was filtered and concentrated *in vacuo* allowing isolation of N-(1-butenyl)-2-pyrrolidinone, **10**[13c] by distillation (9.802 g, 70%). Reaction of 1.85 g (9.74 mmol) of triethyloxonium tetrafluoborate with 1.35 g (9.74 mmol) of **10** gave an oil containing 2.09 g (8.55 mmol, 88%) of 2-ethoxy-*N*-(*E*-1-butenyl)-pyrrolidiniminium tetrafluoroborate:[13b] Dissolution of 0.50 g (1.96 mmol) of 2-ethoxy-*N*-(*E*-1-butenyl)-pyrrolidiniminium tetrafluoroborate in 25 mL of water and stirring for 20 H was followed by filtration and evaporation of the water, *in vacuo*, to give 0.38 g (1.74 mmol, 89%) of ethyl 4-amino-butanoate•HBF_4:[20] ^{1}H NMR (D_2O): δ 1.25 (3H, t, J = 6.0 Hz), 1.80-2.10 (2H, bd t), 2.25-2.55 (2H, bd t), 2.80-3.15 (2H, bd t) and 4.05 ppm (2H, q, J = 6.0 Hz). Addition of this product to 250 mL of saturated aqueous sodium carbonate and heating to reflux for 14 hours resulted in isolation of 0.143 g (1.68 mmol, 86%) of 2-pyrrolidinone.

References

1) T.W. Greene, "Protective Groups in Organic Synthesis," Wiley Interscience, New York (1981); T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed , Wiley Interscience, New York (1991), pp. 397-405.

2) Y. Ohfune and M. Tomita, *J. Am. Chem. Soc.*, **104**, 3511 (1982); D.L. Flynn, R.E. Zelle, and P.A. Grieco, *J. Org. Chem.*, **48**, 2424 (1983).

3) S. Danishefsky, E. Berman, L.A. Clizbe, and M. Hirama, *J. Am. Chem. Soc.*, **103**, 1602 (1981); S. Danishefsky, J. Morris, and L.A. Clizbe, *ibid.*, **103**, 1602 (1981); N. Ikota and A. Hanaki, *Heterocycles*, **22**, 2227 (1984); S. Arita, N.Hirai, Y. Nishimura, and K. Takeshita, *Nippon Kagaku Kaishi*, **1973**, 2160 [*Chem. Abstr.*, **80**: 59122w (1974)].

4) W.Z. Heldt, J. *Am. Chem. Soc.*, **80**, 5880 (1958); C.S. Marvel and W.W. Moyer, Jr., *J. Org. Chem.*, **22**, 1065 (1957); K. Poduška and J. Rudinger, *Coll. Czech. Chem. Commun.*, **22**, 1283 (1957).

5) T. Sato and H. Wakatsuka, *Bull Chem. Soc. Jpn.*, **42**, 1955 (1969); C.A. Grob, H.P. Fischer, W. Raudenbusch, and J. Zergenyi, *Helv. Chim. Acta*, **47**, 1003 (1964).

6) J. Sheu, M.B. Smith, T.Oeschger, and J. Satchell, *Org. Preep. Proceed. Int.*, in press (1992).

7) K.H. Buechel, A.K. Bocz, and F. Korte, *Chem. Ber.*, **99**, 724 (1966); P.A. Cruickshank and J.C. Sheehan *J. Am. Chem. Soc.*, **83**, 2891 (1961); R.M. Rodebaugh and N.H. Cromwell, *J. Heterocyclic Chem.*, **8**, 19 (1971); J.Palecek and J. Kuthan *Z. Chem.*, **17**, 260 (1977); J.A. Deyrup and H.L. Gingrich, *J. Org. Chem.*, **42**, 1015 (1977); M. Malmberg and K. Nyberg, *Acta Chem. Scand, Ser. B*, **B35**, 411 (1981).

8) J.C. Sheehan and R.W. Tulis, *J. Org. Chem.*, **39**, 2264 (1974); J.C. Gramain, R. Remuson, and Y. Troin, *Tetrahedron*, **35**, 759 (1979); W.A. Seth Paul and P.J.A. Demoen, *Bull. Soc. Chim. Belges*, **75**, 524 (1966); M.V. Lock and B.F. Sagar ,*J. Chem. Soc., B, Phys. Org.*, **1966**, 690.

9) E.P. Kramarova,A.G. Shipov, O.B. Artamkina, and Yu.I. Baukov, *Zh. Obshch Khim.*, **54**, 1921 (1984).

10) M. Rothe and T. Toth, *Chem. Ber.*, **99**, 3820 (1966); M.W. Hu., W.E. Bondinell, and D. Hoffmann, *J. Label. Compounds*, **10**, 79 (1974); A.I. Albanov, M.F. Larin, V.A. Pestunovich, M.G. Voronkov, E.P. Kramarova, and Yu.I.Baukov, *Zh. Obshch, Khim.*, **51**, 488 (1981); K.A. Andrianov, A.I. Nogaideli, D.Sh. Akhobadze, and L.M. Khananashvili, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, **1972**, 1150; A.I. Nogaideli, D.Sh. Akhobadze, L.M. Khananashvili, and G.G. Dzhibgashvili, *Soobshch. Akad. Nauk,Gruz, SSR*, **67**, 345 (1972) [*Chem. Abstr.*, **77**: 152258f (1972)].

11) P.J. Reider and E.J.J. Grabowski, *Tetrahedron Lett.*, **26**, 2293 (1982); T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen, and F.A. Bouffard, *J. Am. Chem. Soc.*, **102**, 6161 (1980).

12) M.B. Smith and H.N. Shroff, *J. Org. Chem.*, **49**, 2900 (1984); *Tetrahedron Lett.*, **27**, 2091 (1983).

13) M.B. Smith and H.N. Shroff, *Heterocycles*, **23**, 2229 (1985); C.A. Zezza and M.B. Smith, *J. Org. Chem.*, **53**, 1161 (1988); *Synth. Commun.*, **17**, 729 (1987).

14) R.F. Menezes, C.A. Zezza, J.-L. Sheu, and M.B. Smith ,*Tetrahedron Lett.*, **30**, 3295 (1989).

15) J. Bielawski, S. Brandange, and L. Lindblom, *J. Heterocyclic Chem.*, **15**, 97 (1978); S. Brandange and L. Lindblom, *Acta Chem. Scand. B*, **B30**, 93 (1976)

16) D. Spitzner, *Synthesis*, **1977**, 242.

17) J. Falbe and H.J. Schulze-Steiner, *Brennst. Chem.*, **48**, 136 (1967) [*Chem. Abstr.*, **67**: 73311 (1967)]; H.Möhrle, *Arch. Pharm.* **297**, 474 (1964); B.Puetzer, L. Katz, and L. Horwitz, *J. Am. Chem. Soc.*, **74**, 4959 (1952); F.P. Sidel'kovskaya and F.L. Kolodkin, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, **1965**, 371; M.F. Shostakovskii and F.P. Sidel'kovskaya, *Izvest. Akad. Nauk. SSSR, otdel. Khim. Nauk.*, **1959**, 892; Y. Hachihama and I. Hayashi, *Technol. Rept. Osaka, Univ.*, **4**, 173 (1954) [*Chem. Abstr.*, **49**: 6262a, (1955)]; R. Bacskai, *Acta, Chim. Acad. Sci. Hung.*, **19**, 1 (1959) [*Chem. Abstr.*, **54**: 13097f, (1960)].

18) M.F. Shostakovskii, F.P. Sidel'kovskaya, and M.G. Zelenskaya, *Izvest. Akad. Nauk. SSSR, Otdel. Khim. Nauk*, **1954**, 689 ; J.I. Seeman, *ibid.*, **1977**, 498.

19) Y. Kametori, M. Hojo, R. Masuda, T. Inoue, and T. Izumi, *Tetrahedron Lett.*, **24**, 2575 (1983).

20) K. Bieman, J. Sieble, and F. Capp, *J. Am. Chem. Soc.*, **83**, 3795 (1961).

(Received August 19, 1991)