protected leucine enkephalin **6** was synthesized on a 10-mmol scale within 3–4 h. Total deblocking of the protected pentapeptide by catalytic transfer hydrogenation[12-14] using palladium–carbon and ammonium formate in dioxane–methanol (1:1) gave, in an overall yield of 50–55%, leucine enkephalin **7**[15] which was isolated by filtration, evaporation of solvent, and trituration with ether to remove 9-methylfluorene. Elemental and amino acid analyses, spectral data, and comparison with an authentic sample confirmed the structure of the peptide.

As a test for racemization, a new method[17] was applied which sums the loss of optical activity throughout a complete cycle involving preparation of the Fmoc-protected amino acid (phenylalanine), conversion to its acid chloride, peptide coupling (leucine methyl ester), deblocking by means of 4-(aminomethyl)piperidine, and subsequent N-benzoylation. Overall racemization at the phenylalanine residue, obtained by measuring the ratio of D,L and L,L diastereomers of *N*-benzoylphenylalanylleucine methyl ester using HPLC on silica gel was found to be less than 0.1%.

Acknowledgment. We are indebted to the National Institutes of Health (GM-09706) for support of this work.

Registry No. FMOC-Gly-OH, 29022-11-5; FMOC-Ala-OH, 35661-39-3; FMOC-Ile-OH, 71989-23-6; FMOC-Pro-OH, 71989-31-6; FMOC-Val-OH, 68858-20-8; FMOC-Met-OH, 71989-28-1; FMOC-Cys(Bn)-OH, 53298-33-2; FMOC-Lys(Z)-OH, 86060-82-4; FMOC-Phe-OH, 35661-40-6; FMOC-D-Phe-OH, 86123-10-6; FMOC-Leu-OH, 35661-60-0; FMOC-Tyr(Bn)-OH, 71989-40-7; FMOC-Gly-Cl, 103321-49-9; FMOC-Ala-Cl, 103321-50-2; FMOC-Ile-Cl, 103321-51-3; FMOC-Pro-Cl, 103321-52-4; FMOC-Val-Cl, 103321-53-5; FMOC-Met-Cl, 103321-54-6; FMOC-Cys-(Bn)-Cl, 103321-55-7; FMOC-Lys(Z)-Cl, 103321-56-8; FMOC-Phe-Cl, 103321-57-9; FMOC-D-Cl, 103321-58-0; FMOC-Leu-Cl, 103321-59-1; FMOC-Tyr(Bn)-Cl, 103321-60-4; H-Leu-OBn, 1738-69-8; FMOC-Phe-Leu-OBn, 103321-61-5; H-Phe-Leu-OBn, 63649-15-0; FMOC-Tyr(Bn)-Gly-Gly-Phe-Leu-OBn, 88099-29-0; H-Tyr-Gly-Gly-Phe-Leu-OH, 58822-25-6.

(11) In a typical cycle, to 10 mL of a 0.1 M solution in $CHCl_3$ of the amino acid ester or the peptide ester obtained in a previous step was added 1.1 equiv of the next amino acid chloride in 5–10 mL of $CHCl_3$ along with 10 mL of 10% $NaHCO_3$. After vigorously stirring for 1–10 min, the organic phase was separated, and 0.1–0.5 mL of *N*-methylpiperazine[8] was added with brisk stirring followed by immediate extraction with 5% HCl. To the organic phase was added 3–5 mL of 4-(aminomethyl)piperidine and after 10–30 min the organic phase was extracted twice with 15-mL portions of water or saturated NaCl solution followed by two to four 15-mL portions of 10% phosphate buffer (pH 5.5) to give an organic phase ready for addition of the next amino acid. In case additional organic solvent is added to aid layer separation, the volume of the solution is reduced before continuing.

(12) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929. See also: Carpino, L. A.; Tunga, A. *J. Org. Chem.* **1986**, *51*, 1930.

(13) Atherton, E.; Bury, C.; Sheppard, R. C.; Williams, B. J. *Tetrahedron Lett.*, **1979**, 3041.

(14) Martinez, J.; Tolle, J. C.; Bodanszky, M. *J. Org. Chem.* **1979**, *44*, 3596.

(15) Obtained as tiny white needles on crystallization from methanol: mp 158 °C: $[\alpha]^{25}_D$ −22.8° (*c* 0.8, DMF); lit.[12] mp 155–158 °C lit.[16] mp 206 °C dec; lit.[16] $[\alpha]^{25}_D$ −23.4° (*c* 1, DMF). Anal. Calc for $C_{28}H_{37}N_5O_7 \cdot H_2O$: C, 58.63; H, 6.85; N, 12.21. Found: C, 58.34; H, 6.89; N, 12.19. Amino acid analysis: Tyr 1.05 (1), Gly 2.06 (2), Phe 1.05 (1), Leu 1.00 (1). HPLC: Waters C_{18}-Radialpak (CH_3OH, 1 mL/min): t_R 4.80 min, ref (Chemical Dynamics): 4.81 min. Also obtained in analytically pure form were all acid chlorides in the table and the following precursors and intermediates: (a) Fmoc-Tyr(Bn)-OH, mp 164–166 °C. $[\alpha]^{25}_D$ −15.8° (*c* 1, DMF); (b) Fmoc-Phe-Leu-OBn, mp 154–155 °C $[\alpha]^{25}_D$ −24.7° (*c* 1, DMF); (c) Fmoc-Tyr(Bn)-Gly-Gly-Phe-Leu-OBn, mp 178 °C, $[\alpha]^{25}_D$ −16.9° (*c* = 0.9, DMF). The protected tripeptide [Fmoc-Gly-Phe-Leu-OBn, mp 130 °C $[\alpha]^{25}_D$ −11.5° (*c* = 1, DMF), 80% yield] and the corresponding tetrapeptide [Fmoc-Gly-Gly-Phe-Leu-OBn, mp 163–164 °C, $[\alpha]^{25}_D$ −8.2° (*c* 1, DMF) 63% yield] were also made in single repetitive sequences.

(16) Bower, J. D.; Guest, K. P.; Morgan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2488.

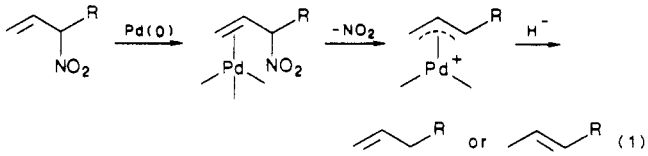
(17) For another application of the method, see: Carpino, L. A.; Rice, N. W.; Mansour, E. M. E.; Triolo, S. A. *J. Org. Chem.* **1984**, *49*, 836.

Louis A. Carpino,* Beri J. Cohen
Kenton E. Stephens, Jr., S. Yahya Sadat-Aalaee
Jien-Heh Tien, Denton C. Langridge
Department of Chemistry
University of Massachusetts
Amherst, Massachusetts 01003
Received February 7, 1986

Regioselective Removal of Allylic Nitro Groups via Hydride Transfer

Summary: Allylic nitro groups are regioselectively removed by hydride-transfer reaction in the presence of a catalytic amount of a palladium catalyst.

Sir: Aliphatic nitro groups serve as activating groups for carbon–carbon bond-forming reactions and their use in organic synthesis depends upon the ease of removal of this activating group. The most important transformation is the replacement of the C–N bond with a C–H bond. In general, reduction of nitro compounds by hydride ion results in bond breaking of a N–O bond rather than a C–N bond.[1] Recently this difficulty has been overcome by radical denitration using tributylstannane and this process is becoming an important synthetic method.[2] However, it is very difficult to control the regiochemistry of denitration of allylic nitro compounds by radical method, where migration of the double bond is a serious problem. In this paper we report a regioselective method for denitration of allylic nitro compounds. The procedure relies on activation by initial complexation with Pd(0) derivatives followed by nitrite ion expulsion and subsequent hydride attack on the resulting π-allyl complex as in eq 1.[3] Various kinds of hydride ion sources appear to be effective and the process is catalytic in the palladium complex.



The results are summarized in Tables I and II. Although reductive replacement of allylic oxygen, sulfur, and selenium functional groups by hydride via catalytic activation by a palladium(0) complex is a well-known reaction,[4] the present denitration is the first example of replacement of the nitro group by hydrogen via hydride transfer. Compared to radical denitration with Bu_3SnH,[5] regiose-

(1) Smith, P. A. S. *The Chemistry of Open-Chain Nitrogen Compounds*, Vol. I and II; W. A. Benjamin Inc.; New York, 1966.

(2) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1075. Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. *Tetrahedron* **1985**, *41*, 4013. Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692 and references therein.

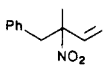
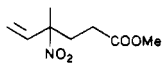
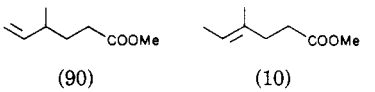
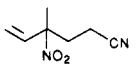
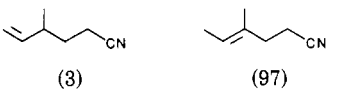
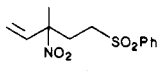
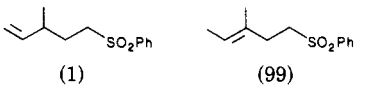
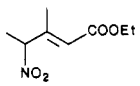
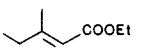
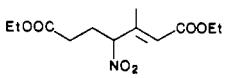
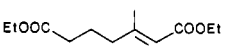
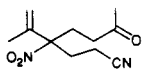
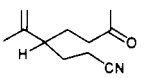
(3) Tamura, R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 3727. Ono, N.; Hamamoto, I.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1982**, 821.

(4) Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett.* **1980**, *21*, 27. Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4382. Matsushita, H.; Negishi, E. *J. Org. Chem.* **1982**, *47*, 4161. Kotake, H.; Yamamoto, T.; Kinoshita, H. *Chem. Lett.* **1982**, 1331.

(5) Radical denitration of the nitro compound of entry 5 gives a mixture of 1-alkene and 2-alkene, whose ratio is 15:85, and this ratio is not affected by the reaction conditions.[2]

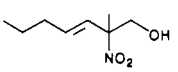
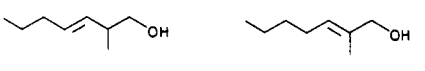
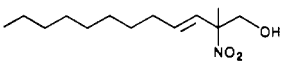
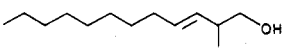
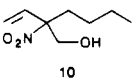
0022-3263/86/1951-3734$01.50/0

Table I. Regioselective Denitration of Allylic Nitro Compounds via Hydride Transfer[a]

entry	R-NO_2	H^-	ligand	solvent	temp, °C	time, h	product (ratio)	yield, %
1	 1	$HCOONH_4$	PPh_3	THF	60	18	 (92) (8)	55
2	1	$NaBH_3CN$	PPh_3	THF	60	17	(32) (68)	98
3	1	$Li(sec\text{-}Bu)_3BH$	PPh_3	THF	20	5	(1) (99)	98
4	1	*n*-BuZnCl	PPh_3	THF	20	20	(0) (100)	86
5	 2	$HCOONH_4$	PPh_3	THF	60	20	 (90) (10)	56
6	2	$NaBH_4$	dppe	THF–*i*-PrOH	20	2	(4) (96)	70
7	 3	$NaBH_4$	dppe	THF–*i*-PrOH	20	2	 (3) (97)	80
8	 4	$NaBH_4$	dppe	THF–*i*-PrOH	20	2	 (1) (99)	73
9	 5	$NaBH_3CN$	PPh_3	THF	60	15	 E/Z = 75/25	70
10	 6	$NaBH_3CN$	PPh_3	THF	60	15	 E/Z = 85/15	71
11	 7	$HCOONH_4$	PPh_3	THF	60	15		58

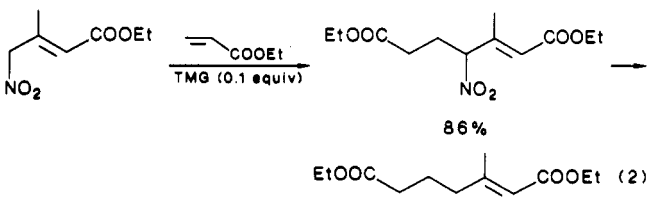
[a] The reaction was carried out in the presence of $Pd(PPh_3)_4$ (5 mol %) and ligands (10 mol %) under Ar. Yields refer to pure isolated products. The ratio of regioisomers of olefins was determined by GLC and NMR. The E/Z ratio was determined by GLC.

Table II. Preparation of Homoallyl Alcohols

entry	R-NO_2	ligand	solvent	temp, °C	time, h	product (ratio)	yield, %
12	 8	PPh_3	THF–*i*-PrOH	0	5	 (97) (3)	86
13	8	dppe	THF–*i*-PrOH	0	5	(75) (25)	80
14	8	PPh_3	THF–*i*-PrOH	20	5	(80) (20)	85
15	 9	PPh_3	THF–*i*-PrOH	0	5		86
16	 10	PPh_3	THF–*i*-PrOH	0	5	 (85) (15)	90

lectivity of denitration by the present method is remarkable. For example, 1-alkenes and 2-alkenes are regioselectively prepared from the allylic nitro compounds by choosing reducing agents and ligands as shown in Table I. Namely, reduction by formate gives 1-alkenes which is the same phenomena as in reduction of allyl acetates.[6] When good nucleophilic hydride sources such as $NaBH_4$ and smaller ligands such as (diphenylphosphino)ethane (dppe) are used, 2-alkenes are produced regioselectively (entries 1–8).

The regiochemistry of hydride approach to the π-allyl unit is controlled by both the nature of the π-allyl unit substituents and the steric nature of the nucleophiles and the ligands. When electron-withdrawing substituents such as COOR are used, hydride ions attack the remot site to give α,β-unsaturated esters regioselectively. The example of entry 11 is noteworthy, since both steps proceed with high regioselectivity (eq 2).

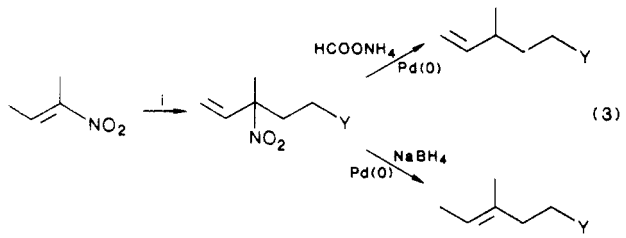


(2)

Thus, the nitro group can be removed after it serves as

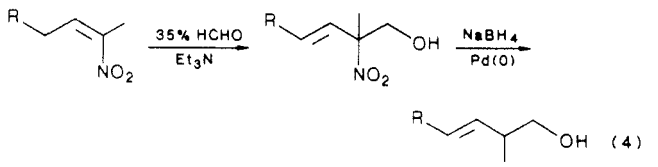
(6) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613.

an activating group for carbon–carbon bond-forming reactions. Since the carbanions of allylic nitro compounds are produced from nitroolefins, the present denitration provides a useful synthetic methods. For example, 2-nitro-2-butene reacted with electron-deficient olefins in the presence of tetramethylguanidine (TMG, 0.1 equiv) to give the allylic nitro compounds, which were converted into 1-alkenes or 2-alkenes, respectively, as shown in entries 5–8.



Y = COOMe, CN, SO_2Ph
(i) CH_2=CHY, TMG (0.1 equiv), rt, 24 h

Base-catalyzed reaction of nitroolefins with aldehydes followed by denitration provides a new synthetic method of homoallyl alcohols (Table II). The reaction of nitroolefins with aldehydes was carried out by stirring a mixture of nitroolefins, 37% HCHO, and triethylamine (0.1 equiv) in acetonitrile at 20 °C for 15 h. Hydroxymethylated allylic nitro compounds were obtained in 80–90% yield by this procedure. Denitration was carried out by stirring a mixture of allylic nitro compounds, $NaBH_4$ (1.2 equiv), $Pd(PPh_3)_4$ (5 mol %), and PPh_3 (10 mol %) in THF–*i*-PrOH (1/1) at 0 °C for 5 h. When the reaction was carried out at 20 °C (entry 14) or dppe was used instead of PPh_3 (entry 13), the selectivity of the formation of homoallylic alcohols was poor. The results are summarized in Table II.



Registry No. 1, 83659-69-2; 2, 81769-17-7; 3, 103621-19-8; 4, 103621-20-1; 5, 103621-21-2; 6, 103621-22-3; 7, 103621-23-4; 8, 103621-24-5; 9, 103621-25-6; 10, 103621-26-7; $PhCH_2CH(CH_3)$-CH=CH_2, 1647-06-9; $PhCH_2C(CH_3)$=$CHCH_3$, 40296-93-3; H_2-C=$CHCH(CH_3)(CH_2)_2CO_2CH_3$, 90112-90-6; H_3CCH=$C(C$-$H_3)(CH_2)_2CO_2CH_3$, 97764-27-7; H_2C=$CHCH(CH_3)(CH_2)_2CN$, 100859-65-2; H_3CCH=$C(CH_3)(CH_2)_2CN$, 22117-92-6; H_2C=$CHCH(CH_3)(CH_2)_2SO_2Ph$, 103621-27-8; H_3CCH=$C(CH_3)$-$(CH_2)_2SO_2Ph$, 103621-28-9; (*E*)-$H_3CCH_2C(CH_3)$=$CHCO_2Et$, 13979-44-7; (*Z*)-$H_3CCH_2C(CH_3)$=$CHCO_2Et$, 13979-16-3; (*E*)-$EtO_2C(CH_2)_3C(CH_3)$=$CHCO_2Et$, 103621-29-0; (*Z*)-EtO_2-$(CH_2)_3C(CH_3)$=$CHCO_2Et$, 103621-30-3; H_2C=$C(CH_3)CH(C$-$H_2)_2CN(CH_2)_2COCH_3$, 103621-31-4; $H_3C(CH_2)_2CH$=$CHCH(C$-$H_3)CH_2OH$, 102877-67-8; $H_3C(CH_2)_3CH$=$C(CH_3)CH_2OH$, 37616-08-3; $H_3C(CH_2)_7CH$=$CHCH(CH_3)CH_2OH$, 103621-32-5; H_2C=$CHCH(CH_2OH)(CH_2)_3CH_3$, 53045-66-2; H_3CCH=$C(C$-$H_2OH)(CH_2)_3CH_3$, 21645-15-8; $H_3C(CH_2)_2CH$=$CHCH(NO_2)CH_3$, 103621-33-6; $H_3C(CH_2)_7CH$=$CHCH(NO_2)CH_3$, 103621-34-7; H_2C=$CHCH(NO_2)(CH_2)_3CH_3$, 103621-35-8.

Noboru Ono,* Isami Hamamoto
Akio Kamimura, Aritsune Kaji

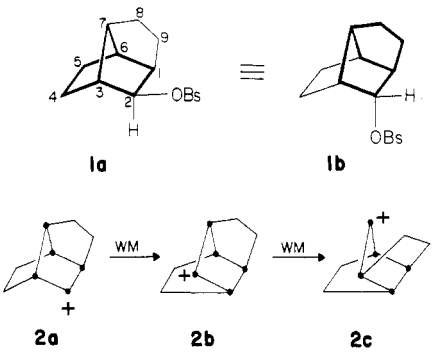
Department of Chemistry
Faculty of Science, Kyoto University
Kyoto 606, Japan

Received May 9, 1986

Ionization of 2-Brexyl Brosylate: An Exo-Like Rate without Symmetrical Bridging

Summary: 2-Brexyl brosylate and *exo*-norbornyl brosylate show similar ionization rates but differ markedly with respect to internal return, secondary isotope effect, and optical activity.

Sir: A central issue in norbornyl solvolyses is whether high exo/endo rate ratios stem largely from exalted exo or from suppressed endo rates.[1] Either view can be supported by judicious selection of reference standards.[1,2] In a brexane skeleton, a substituent at C-2 is simultaneously exo to one norbornyl unit and endo to another (note: **1a** is superposable on **1b**).[3] Therefore, whether **1** has the ionization character of an *exo*- or an *endo*-norbornyl derivative is of considerable interest. Like its norbornyl counterpart, a σ-bridged (i.e., nonclassical) 2-brexyl cation has a plane of symmetry and the localized (i.e., classical) structure (**2a**) is chiral. A degenerate Wagner-Meerwein (WM) rearrangement (**2a** ⇌ **2b**) converts the classical form to its mirror image. And repetitive WM (i.e., **2a** → **2b** → **2c** → etc.) alternates the chirality and can transfer the positive charge to every carbon of a core ring (shown by bold dots).



We recently developed an improved synthesis of brexan-2-one[4] and now report studies of buffered acetolysis of 2-brexyl brosylate (**1**), of its 2-deuterated analogue, and of its optically active form. The product acetates arise from two rearranged ions, viz. **3** and **4**. Consequently, it was essential to investigate also the exo and endo epimers of 4-brexyl brosylate (**5**) and of 2-brendyl brosylate (**6**).

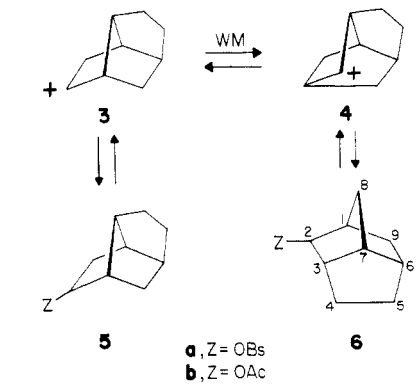


Table I summarizes our findings and also includes our own

(1) Recent reviews: (a) Barkhash, V. A. *Top. Curr. Chem.* **1984**, *116/117*, 1–265. (b) Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426–431. (c) Brown, H. C. *Ibid.* **1983**, *16*, 432–440. (d) Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Ibid.* **1983**, *16*, 440–448. (e) Walling, C. *Ibid.* **1983**, *16*, 448–454. (f) Kirmse, W. *Top. Curr. Chem.* **1979**, *80*, 125–331.

(2) Brown, H. C. *The Nonclassical Ion Problem*, with comments by Schleyer, P. v. R.; Plenum: New York, 1977; Chapter 8.

(3) Nickon, A.; Kwasnik, H. R.; Mathew, C. T.; Swartz, T. D.; Williams, R. O.; DiGiorgio, J. B. *J. Org. Chem.* **1978**, *43*, 3904–3916.

(4) Nickon, A.; Stern, A. G. *Tetrahedron Lett.* **1985**, *26*, 5915–5918.

0022-3263/86/1951-3736$01.50/0