sulfate and magnesium sulfate, and concentrated in vacuo to afford 717 g of a thick golden oil.

Hexanes (700 mL) was added to the oil and the mixture heated until a clear yellow solution was obtained. The solution was allowed to cool and the flask scratched to induce crystallization. The vessel was cooled in a refrigerator for ca. 20 h. The solid was filtered off, washed with a small amount of cold hexanes, and dried in vacuo. The resulting solid was recrystallized from 400 mL of hexanes to afford 176 g of pure 3*R*,4*S* material **7**. The combined mother liquors from above were concentrated under reduced pressure and the enriched mixture was completely separated by preparative HPLC using a Waters Prep 500 utilizing two silica gel packs and 9% acetone in hexanes as the eluant (flow rate 250 mL/min). The appropriate fractions were combined and the solvents evaporated under reduced pressure. These procedures afforded 245 g (40%) of the desired 3*S*,4*S* isomer **6** and 266 g (43%) of the 3*R*,4*S* isomer **7**.

(3*S*,4*S*)-6: mp 67-69 °C; R_f 0.35 (20% acetone in hexanes); $[\alpha]_D$ -32° (*c* 1.4, MeOH) (lit.[2] -37°); NMR ($CDCl_3$; 300 MHz) δ 0.80-1.92 (m containing 3-H t at δ 1.28 and 9-H s at δ 1.44, 13 H), 2.40-2.62 (m, 2 H), 3.26 (br s, 1 H), 3.60-3.70 (m, 1 H), 4.01 (d, J = 9.0 Hz, 1 H), 4.18 (q, 2 H), 4.69 (d, J = 9.6 Hz, 1 H); IR ($CHCl_3$) 3460 (br), 2940, 1705, 1490, 1165 cm^{-1}.

(3*R*,4*S*)-7: mp 81-83 °C; R_f 0.25 (20% acetone in hexanes); $[\alpha]_D$ -16.7° (*c* 1.6, MeOH); NMR ($CDCl_3$; 300 MHz) δ 0.70-1.92 (m, containing 3-H t at δ 1.28 and 9-H s at δ 1.45, 13 H), 2.41-2.52 (m, 2 H), 3.40 (br s, 1 H), 3.62-3.78 (m, 1 H), 4.00 (m, 1 H), 4.17 (q, 2 H), 4.54 (d, J = 10.2 Hz, 1 H); IR ($CHCl_3$) 450 (br), 2930, 1700, 1485, 1445, 1370, 1165, 1030 cm^{-1}.

Acknowledgment. We thank Drs. David Melillo and David Tschaen for helpful discussions regarding the two-carbon homologation procedure. We also express our appreciation to Drs. Daniel Rich and Jurgen Maibaum for performing the ee analysis and for sharing their results with us prior to publication.

Registry No. **2**, 63-91-2; **3**, 27527-05-5; **4**, 37736-82-6; **5**, 112151-92-5; **6**, 98105-43-2; **7**, 98105-44-3; $EtOCOCH_2COOH$, 1071-46-1.

Methyl Ester Nonequivalence in the ^1H NMR Spectra of Diastereomeric Dipeptide Esters Incorporating N-Terminal α-Phenylglycine Units

Louis A. Carpino

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

Received July 13, 1987

Numerous methods for following racemization during peptide coupling reactions have been reported.[1] Techniques based on NMR spectroscopy have the advantage of simplicity and rapid applicability and are therefore especially suited for quick survey work where high sensitivity is not required. The first such test, described by Halpern and Weinstein,[2] took advantage of the *C*-methyl doublets arising from alanine units built into various protected diastereomeric dipeptides. Davies, Thomas, and Williams[3] subsequently recommended the use of *N*-benzoyl dipeptide methyl esters since different methyl ester singlets were observed in many such cases and the appropriate peaks occur in an uncluttered region of the spectrum. While not limited to a specific amino acid such as alanine, the Davies method requires the presence of a terminal *N*-benzoyl substituent and thus diastereomeric dipeptide methyl esters bearing classic urethane-type protecting groups such as benzyloxycarbonyl, *tert*-butyloxycarbonyl, or (9-fluorenylmethyl)oxycarbonyl do not exhibit nonequivalence. Visualization of the effect in such cases requires deblocking and subsequent benzoylation.

While surveying conditions which might lead to racemization during the coupling of various FMOC amino acid chlorides,[4] we initially examined a moderately sensitive model, FMOC phenylalanine chloride, with the coupling step being followed by 4-(aminomethyl)piperidine (4-AMP) deblocking and N-benzoylation. In order to magnify the susceptibility to racemization[5] we subsequently shifted to a study of analogous reactions of the FMOC derivative of α-phenylglycine chloride. Although a nonprotein amino acid, α-phenylglycine is readily available in both L and D forms and its selection proved to be especially fortunate. Initial studies involved reaction of [(9-fluorenylmethyl)-oxycarbonyl]-L- and [(9-fluorenylmethyl)oxycarbonyl]-D-α-phenylglycine chlorides with alanine methyl ester followed by in situ examination of the reaction mixtures by ^1H NMR analysis. The *C*-methyl doublets of the diastereomeric dipeptides **1** differed as expected from the work of Weinstein and co-workers.[2] However, we were pleas-

FMOC-(L or D)-Phg-Ala-OMe
1

antly surprised to find that, in addition, the methyl ester singlets were also well separated (δ 3.59, 3.66). Indeed the separation for these *urethanes* (0.07 ppm) is about the same as observed by Davies and co-workers[3] for a variety of related *N*-benzoyl derivatives (range ca. 0.04-0.1 ppm). These ester peaks were also well separated in DMSO-d_6, a result which contrasts with the previous recommendation that all traces of polar solvents be removed prior to NMR measurement in view of coalascence of the two peaks in such media.

The effect observed appears general for dipeptides bearing other C-terminal amino acid units. In some cases the diastereomeric pairs were isolated and characterized; in other cases reaction products were examined in solution (see Table I and Experimental Section). That the effect arises from the presence of the α-phenyl substituent at the N-terminal amino acid position and is unrelated to any particular N-terminal acyl function is confirmed by the observation of two widely separated methyl ester peaks in the cases of a number of other diastereomeric N-substituted dipeptide derivatives **2** (X = BOC, Z, Ts; X_{aa} = Ala or Phe) as well as a free amino dipeptide methyl ester (**2**, X = H; X_{aa} = Phe).

X-Phg-X_{aa}-OMe
2

(1) Reviews: (a) Kemp, D. S. In *The Peptides. Analysis, Synthesis, Biology*; Gross, E., Meienhofer, J., Eds.; Academic: New York, 1979; Vol. 1, p 315. (b) Benoiton, N. L. In *The Peptides. Analysis, Synthesis, Biology*; Gross, E., Meienhofer, J., Eds.; Academic: New York, 1983; Vol. 5, p 217.

(2) (a) Halpern, B.; Chew, L. F.; Weinstein, B. *J. Am. Chem. Soc.* **1967**, *89*, 501. (b) Halpern, B.; Nitecki, D. E.; Weinstein, B. *Tetrahedron Lett.* **1967**, 3075. (c) Weinstein, B.; Pritchard, A. E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1015.

(3) (a) Davies, J. S.; Thomas, R. J.; Williams, M. K. *Chem. Commun.* **1975**, 76. (b) Davies, J. S.; Mohammed, A. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2982. (c) Davies, J. S.; Thomas, R. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1639. (d) Davies, J. S.; Hakeem, E. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1387.

(4) (a) Carpino, L. A.; Cohen, B. J.; Stephens, K. E., Jr.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732. (b) Beyermann, M.; Bienert, M.; Repke, H.; Carpino, L. A. In *Peptides 1986. Proceedings of the 19th European Peptide Symposium*; Theodoropoulos, D., Ed.; de Gruyter: New York, 1987; p 107.

(5) Compare (a) Smith, G. G.; Sivakua, T. *J. Org. Chem.* **1983**, *48*, 627. (b) Stroud, E. D.; Fife, D. J.; Smith, G. G. *J. Org. Chem.* **1983**, *48*, 5368.

0022-3263/88/1953-0875$01.50/0

Table I. Protected Dipeptide Esters

dipeptide	preparative method	yield, %[a]	mp, °C	α_D, deg [t]	^{1}H NMR of MeO (or t-BuO) group, δ in $CDCl_3$ (in CD_3SOCD_3)[b]	mol. formula	anal. data calcd/found C	H	N
Z-Phg-Phe-OCH_3	*c*	80.2	153–155	+82.0 (*c* 0.44, CH_2Cl_2) [28]	3.56	$C_{26}H_{26}N_2O_5$	69.95	5.83	6.27
							69.82	5.83	6.23
Z-D-Phg-Phe-OCH_3	*c*	82.0	168–170	−5.68 (*c* 0.44, CH_2Cl_2) [28]	3.64	$C_{26}H_{26}N_2O_5$	69.95	5.83	6.27
							69.55	6.17	6.34
Z-Phg-Phe-$OC(CH_3)_3$	*c*	80.0	123–124	+74.3 (*c* 0.4, CH_2Cl_2) [28]	1.30 (Me_3CO)	$C_{29}H_{32}N_2O_5$	71.31	6.55	5.73
							71.29	6.49	5.69
Z-D-Phg-Phe-$OC(CH_3)_3$	*c*	95.0	139–141	−9.28 (*c* 0.7, CH_2Cl_2) [28]	1.39 (Me_3CO)	$C_{29}H_{32}N_2O_5$	71.31	6.55	5.73
							71.16	6.57	5.68
Ts-Phg-Ala-OCH_3	*d*	91.9	202–204	+100.3 (*c* 0.4, CH_2Cl_2) [28]	3.66	$C_{19}H_{22}N_2O_5S$	58.46	5.64	7.17
							58.40	5.69	7.01
Ts-D-Phg-Ala-OCH_3	*d*	75.0	174–175	−103.3 (*c* 0.4, CH_2Cl_2) [27]	3.72	$C_{19}H_{22}N_2O_5S$	58.46	5.64	7.17
							58.24	5.75	7.15
FMOC-Phg-Phe-OCH_3	*d*	80.0	194–194.5	+22.2 (*c* 0.5, DMF) [28]	3.62	$C_{33}H_{30}N_2O_5$	74.15	5.61	5.24
							73.92	5.91	5.17
FMOC-D-Phg-Phe-OCH_3	*d*	80.0	192–194	−21.6 (*c* 0.5, DMF) [28]	3.72	$C_{33}H_{30}N_2O_5$	74.15	5.61	5.24
							74.14	5.55	5.25
BOC-Phg-Phe-OCH_3	*e*				3.57				
BOC-D-Phg-Phe-OCH_3	*e*				3.71				
Bz-Phg-Ala-OCH_3	*c*	86.1	186–187	+53.5 (*c* 1, EtOAc) [25]	3.59 (3.57)	$C_{19}H_{20}N_2O_4$	67.05	5.88	8.23
							66.90	5.75	8.10
Bz-D-Phg-Ala-OCH_3	*c*	89.0	190–191	−65.0 (*c* 0.1, EtOAc) [25]	3.64 (3.64)	$C_{19}H_{20}N_2O_4$	67.05	5.88	8.23
							67.08	5.85	8.29
H-Phg-Phe-OCH_3·CF_3CO_2H	*e*				3.84[f] (3.50)				
H-D-Phg-Phe-OCH_3·CF_3CO_2H	*e*				3.95[f] (3.66)				

[a] The yield given is of material purified by recrystallization from EtOAc–hexane. In the case of FMOC-D-Phg-Phe-OMe, EtOAc–$EtNO_2$ (1:1) was used for recrystallization. [b] The solvent for ^{1}H NMR analysis was $CDCl_3$ except for figures given in parentheses which were measured in CD_3SOCD_3. [c] Prepared according to the general method of B. Belleau and G. Malek (*J. Am. Chem. Soc.* **1968**, *90*, 1651) from the protected amino acid, EEDQ, the amino acid ester hydrochloride, and Et_3N in THF. [d] Prepared from Ts-L- or Ts-D-Phg-Cl or FMOC-L- or FMOC-D-Phg-Cl by two-phase coupling in CH_2Cl_2–$NaHCO_3$–H_2O according to ref 4. [e] Generated in situ as described in Experimental Section. [f] The solvent was CF_3CO_2H–$CDCl_3$ (2.5/1).

Interestingly in the case of a set of tosyl dipeptides (**2**, X = Ts; X_{aa} = Ala) the Halpern–Weinstein alanine *C*-methyl doublets are not separated. In one case, that of the benzyloxycarbonyl derivatives **3**, a set of methyl and *tert*-butyl esters were compared. Remarkably the separation (Δ = 0.08–0.09 ppm) was about the same in both cases.

Z-Phg-Phe-OR
3

a, R = Me; **b**, R = CMe_3

Davies and Hakeem[3d] suggested that the methyl ester peaks of the two *N*-benzoyl diastereomers differ because of the relative shielding effects manifested in the hydrogen-bonded, cyclic, seven-ring structures assumed to be favored in nonpolar solvents with the DL form always upfield of the LL isomer. In contrast, the α-phenylglycine-derived dipeptides show the LL peak upfield with the shielding effects being determined principally by the relative positioning of the α-phenyl and carboalkoxy substituents. It is therefore expected that an *N*-benzoyl dipeptide methyl ester bearing α-phenylglycine at the N-terminal position should show a reduced separation of the diastereomeric methyl ester peaks in a solvent such as $CDCl_3$ whereas in DMSO-d_6, due to destruction of cyclic, H-bonded structures,[6] the separation should be enhanced. This is in fact observed, with separation of the methyl ester singlets in the case of *N*-benzoyl derivative **2** (X = C_6H_5CO; X_{aa} = Ala) being approximately 0.05 and 0.07 ppm in $CDCl_3$ and DMSO-d_6, respectively.

Using these simple tests, it was shown that FMOC-substituted α-phenylglycine chloride couples with either phenylalanine or alanine methyl ester under the normal two-phase conditions (CH_2Cl_2/$NaHCO_3$/H_2O) of our rapid FMOC/4-AMP peptide segment synthesis[4] without significant racemization. Similar results were observed in homogeneous media, e.g., by addition of the acid chloride to a solution of the methyl ester hydrochloride in the presence of 2 equiv of triethylamine.

Experimental Section[7]

***N*-[(9-Fluorenylmethyl)oxycarbonyl]-α-phenylglycine Chloride.** A suspension of 750 mg of FMOC-Phg-OH [mp 175.5–177 °C; α^{28}_D +87.1° (*c* 1, MeOH); lit.[8] mp 169 °C; lit.[8] α^{20}_D +91.7° (*c* 1, MeOH)] in 5 mL of CH_2Cl_2 and 1.5 mL of thionyl chloride was stirred at room temperature. After 6 h a clear solution had formed but subsequently the acid chloride began to precipitate. After a total of 24 h the mixture was rotary evaporated, and the residual yellow solid was triturated and washed onto a filter funnel with hexane. There was obtained 600 mg (76.2%) of the acid chloride as a yellow powder, mp 138–140 °C dec. A few crystals were added to methanol and spotted on a TLC plate. Elution with 35% EtOAc in hexane showed no residual free acid. Recrystallization from CH_2Cl_2–hexane (1:3) gave tiny yellow crystals: mp 138–140 °C dec; α^{28}_D +114.2° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.1–4.5 (m, 3, $CHCH_2O$), 5.55 (br s, 2, CH, NH), 7.1–7.8 (m, 14, aryl).

Anal. Calcd for $C_{23}H_{18}ClNO_3$: C, 70.49; H, 4.59; N, 3.57. Found: C, 70.19; H, 4.65; N, 3.57.

***N*-[(9-Fluorenylmethyl)oxycarbonyl]-D-α-phenylglycine Chloride.** The title compound was obtained as described for the L isomer from 750 mg of FMOC-D-Phg-OH [mp 175.5–176.5 °C, α^{28}_D −86.9° (*c* 1, MeOH)], which gave 620 mg (78.8%) of the acid chloride as a yellow powder. Recrystallization gave tiny yellow needles: mp 138–140 °C dec; α^{28}_D −115.6° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.15–4.55 (m, 3, $CHCH_2O$), 5.5 (br s, 2, CH, NH), 7.15–7.76 (m, 14, aryl).

Anal. Calcd for $C_{23}H_{18}ClNO_3$: C, 70.49; H, 4.59; N, 3.57. Found: C, 70.27; H, 4.78; N, 3.54.

Generation of BOC-Phg-Phe-OMe and H-Phg-Phe-OMe·CF_3CO_2H. To a solution of 90 mg of FMOC-Phg-Phe-OMe in 2.5 mL of CH_2Cl_2 there was added 1.5 mL of 4-AMP and the solution stirred at room temperature for 20 min and diluted with 25 mL of $CHCl_3$. The solution was extracted with 10 mL of water followed by four 10-mL portions of phosphate buffer of pH 5.5. After drying ($MgSO_4$) the organic layer was rotary evaporated at room temperature to give a white solid, which was dissolved in 5.0 mL of CH_2Cl_2 containing 50 mg of $(BOC)_2O$. After 15 h the solution was washed with 10 mL of 5% hydrochloric acid and 10 mL of 0.5 M sodium bicarbonate, dried ($MgSO_4$), and rotary evaporated at room temperature to give 60 mg of a white solid. ^1H NMR examination in $CDCl_3$ showed a spectrum which agreed with that expected for the BOC dipeptide ester except that an extraneous peak (δ 1.52) due to some residual $(BOC)_2O$ appeared. The latter was removed by allowing the solid to stand in an open beaker for about 48 h. The remaining residue was added to 0.5 mL of CF_3CO_2H in an NMR tube in order to effect deblocking of the BOC group. After 1 h 0.2 mL of $CDCl_3$ containing 1% TMS was added. ^1H NMR analysis showed that deblocking was complete, the new methyl ester peak appearing at δ 3.84. The contents of the NMR tube were evaporated and the residual solid dissolved in DMSO-d_6 whereby the methyl resonance now appeared at δ 3.50. A similar reaction sequence was carried out starting from FMOC-D-Phg-Phe-OMe in which case the new methyl ester resonance appeared at δ 3.95 and 3.66 in CF_3CO_2H and DMSO-d_6, respectively. The latter position agrees with that recorded (δ 3.65) for the corresponding D,L-hydrochloride in DMSO-d_6.[9]

***N*-(*p*-Tolylsulfonyl)-α-phenylglycine Chloride.** A suspension of 750 mg of Ts-Phg-OH [mp 175–177 °C; α^{28}_D +125.4° (*c* 1, dioxane)] in 5 mL of CH_2Cl_2 was treated with 1.2 mL of $SOCl_2$ and the mixture refluxed with stirring for 1 h, which eventually gave a clear yellow solution. Rotary evaporation gave a yellow solid, which was triturated with hexane and washed onto a filter plate to give 644 mg (81%) of the acid chloride as a colorless solid, mp 134–137 °C dec. TLC showed no residual free acid (see above comment on FMOC analogue). The analytical sample was recrystallized from CH_2Cl_2–hexane (1:3): mp 133–136 °C dec; α^{27}_D +136.6° (*c* 1, CH_2Cl_2), +154.0° (*c* 0.5, dioxane); ^1H NMR ($CDCl_3$) δ 2.42 (s, 3, CH_3), 5.41 (d, 1, CH), 5.84 (br d, 1, NH), 7.2–7.8 (m, 9, aryl).

Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.32; N, 4.32. Found; C, 55.83; H, 4.27; N, 4.43.

***N*-(*p*-Tolylsulfonyl)-D-α-phenylglycine Chloride.** As described above for the L-isomer 600 mg of the acid [mp 179–181 °C, α^{28}_D −123.8° (*c* 1, dioxane)] was refluxed in 4.5 mL of CH_2Cl_2 and 1.5 mL of $SOCl_2$. Workup gave 520 mg (81.7%) of the acid chloride as a yellow powder. Recrystallization from CH_2Cl_2–hexane (1:3) gave yellow-white crystals: mp 133–136 °C dec; α^{27}_D −152.6° (*c* 0.5, dioxane), −136.2° (*c* 1, CH_2Cl_2); lit.[10] mp 155 °C; lit.[10] α^{30}_D −88° (*c* 1, dioxane); ^1H NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3), 5.35 (d, 1, CH), 5.9 (br d, 1, NH), 7.14–7.75 (m, 9, aryl).

Coupling Reactions of FMOC-D- or FMOC-L-α-Phg-Cl. To a solution of 165 mg of NEt_3 and 225 mg of H-Phe-OMe·HCl in 10 mL of CH_2Cl_2 there was added over ca. 30 s 293.7 mg of FMOC-D-Phg-Cl. After a few minutes the mixture was washed twice with 5-mL portions of 5% HCl and once with 5 mL of 1 M $NaHCO_3$. After drying ($MgSO_4$) evaporation gave 390 mg (97.3%) of the DL dipeptide as a slightly yellowish colored solid, mp 186–190 °C. Recrystallization from EtOAc–$EtNO_2$ (1:1) gave 330 mg (82.3%) of the pure material, mp 190–192 °C. ^1H NMR examination of the crude material prior to crystallization showed no evidence (<2–3%, 60-MHz spectrometer, or <1%, 200-MHz spectrometer) for any of the LL diastereomer. Similar results were

(6) Compare Toniolo, C.; Bonora, G. M.; Stavropoulos, P. C.; Theodoropoulos, D. *Biopolymers* **1986**, *25*, 289.

(7) Melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer 237B and ^1H NMR spectra on Varian A-60A, Perkin-Elmer R-12, and Varian XL-200 instruments with Me_4Si as internal standard. Elemental analyses were carried out by the University of Massachusetts Microanalytical Laboratory under the direction of Greg Dabkowski. Thin-layer chromatography was performed on aluminum-backed Merck silica gel 60 F254 plates.

(8) Kessler, H.; Kuhn, M.; Loschner, T. *Justus Liebigs Ann. Chem.* **1986**, 1.

(9) Heuser, L. J.; Anderson, C. F.; Applegate, H. E.; Böhme, E. H.; Dolfini, J. E.; Puar, M. S. *J. Org. Chem.* **1974**, *39*, 3929.

(10) Khunt, V. N.; Parikh, A. R. *J. Inst. Chem. (India)* **1978**, *50*, 27.

obtained starting from FMOC-L-Phg-Cl and also when the coupling of either the D or L isomer was carried out by the two-phase method (CH_2Cl_2–$NaHCO_3$–H_2O) with H-Phe-$OCMe_3$, H-Phe-OMe, or H-Ala-OMe. See table I for characterization data.

Acknowledgment. We thank the National Science Foundation (NSF CHE-8609176) and the National Institutes of Health (GM-09706) for support of this work, Mr. S. Y. Sadat-Aalaee for purification of some of the intermediates and determination of specific rotations, and Mr. Hann Guang Chao for the high-field NMR spectra.

Registry No. Z-Phg-Phe-OCH_3, 111524-81-3; Z-D-Phg-Phe-OCH_3, 81819-48-9; Z-Phg-Phe-$OC(CH_3)_3$, 111524-82-4; Z-D-Phg-Phe-$OC(CH_3)_3$, 111524-83-5; Ts-Phg-Ala-OCH_3, 111524-84-6; Ts-D-Phg-Ala-OCH_3, 111524-85-7; FMOC-Phg-Phe-OCH_3, 111524-86-8; FMOC-D-Phg-Phe-OCH_3, 111524-87-9; BOC-Phg-Phe-OCH_3, 111524-88-0; BOC-D-Phg-Phe-OCH_3, 94778-64-0; Bz-Phg-Ala-OCH_3, 111524-89-1; Bz-D-Phg-Ala-OCH_3, 111524-90-4; H-Phg-Phe-OCH_3·CF_3COOH, 111524-92-6; H-D-Phg-Phe-OCH_3·CF_3COOH, 111524-94-8; FMOC-Phg-OH, 102410-65-1; FMOC-D-Phg-OH, 111524-95-9; FMOC-Phg-Cl, 111524-96-0; FMOC-D-Phg-Cl, 111524-97-1; Ts-Phg-OH, 111524-98-2; Ts-Phg-Cl, 111524-99-3; Ts-D-Phg-OH, 60712-47-2; Ts-D-Phg-Cl, 63406-97-3; H-Phe-OCH_3·HCl, 7524-50-7; H-Phg-Phe-OCH_3, 111524-91-5.

A Simple, Efficient, and Highly Selective Method for the Regeneration of Carbonyl Compounds from Oximes and Semicarbazones

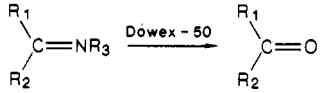
Brindaban C. Ranu* and Dipak C. Sarkar

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700 032, India

Received June 17, 1987

Regeneration of carbonyl compounds from their oximes, semicarbazones, and other derivatives under mild conditions has recently[1a-e,2a] received much attention. Classically, it involved hydrolytic cleavage by exchange[3] under acidic conditions (phthalic anhydride–water,[3a] H^+/pyruvic acid,[3b,c] aqueous oxalic acid,[3d] nitrous acid,[3e] levulinic acid–aqueous hydrochloric acid,[3f] hydrochloric acid–formaldehyde,[3g] aqueous acetic acid,[3h] sodium hydrogen sulfite[3i]). Since these methods exclude acid-sensitive ketones and aldehydes, a variety of oxidative[1] (cetyltrimethylammonium permanganate (CTAP),[1a] (diacetoxyiodo)benzene,[1b] chromyl chloride,[1c] potassium bromate,[1d] dinitrogen tetroxide,[1e] pyridinium chlorochromate,[1f] chromium(VI) oxide in the form of Jones and Collins reagent,[1g] lead(IV) acetate,[1h] ozone,[1i] cerium(IV) ammonium nitrate,[1j] nitrosochloride–pyridine,[1k] nitronium and nitrosonium salts,[1l] Barton's reagent,[1m] bromine,[1n] alkaline hydrogen peroxide,[1o] periodic acid,[1g] bis(pyridinesilver) permanganate,[1p] bis(triphenylphosphine)palladium/oxygen,[1q] sodium nitrite,[1r] thallium(III) nitrate,[1s] thallium(III) acetate[1t]) and reductive[2] (pentacarbonyl iron,[2a-c] aluminum triisopropoxide,[2d] titanium(III) chloride,[2e] chromium(II) acetate,[2f] zinc–acetic acid,[2g] Raney nickel alloy in alkaline solution (nascent hydrogen)[2h]) procedures have been developed over the years. These methods, though satisfactory for simple molecules, often are less useful for complex molecules because of (a) oxidation or reduction of other easily oxidizable or reducible groups present in the molecule and (b) overoxidation or overreduction of the lib-

Scheme I[a]



[a] R_1 = alkyl; R_2 = alkyl or H; R_3 = OH, or $NHCONH_2$.

Table I. Cleavage of Oximes and Semicarbazones with Dowex-50

entry	regenerated carbonyl compounds[a]	refluxing time (h)	yield (%)[b]
1	cyclohexanone	2	87[c]
			90[d]
2	acetophenone	1	90[c]
			96[d]
3	indanone	2	85[c]
			91[d]
4	benzophenone	3	85[c]
			90[d]
5	benzaldehyde	5	32[c]
			20[d]
6	*m*-methoxybenzaldehyde	5	30[c]
			26[d]
7	citral	8	no reactn
8	ethyl 2-oxacyclohexanecarboxylate	3	74[c]
			76[d]
9	ethyl 2-oxacyclopentanecarboxylate	3	75[c]
			78[d]
10	4-carbethoxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester)	3	80[c]
			85[d]

[a] The regenerated carbonyl compounds are compared with the authentic samples (TLC, IR, NMR). [b] Yield refers to isolated products. [c] Carbonyl compounds obtained from oximes. [d] Carbonyl compounds obtained from semicarbazones.

(1) (a) Vankar, P.; Rathore, R.; Chandrasekaran, S. *J. Org. Chem.* **1986**, *51*, 3063. (b) Moriarty, R. M.; Prakash, O.; Vavilikolanu, R. *Synth. Commun.* **1986**, *16*, 1247. (c) Salmon, M.; Miranda, R.; Angeles, E. *Synth. Commun.* **1986**, *16*, 1827. (d) Narayanan, S.; Srinivasan, V. S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1557. (e) Shim, S. B.; Kim, K.; Kim, Y. H. *Tetrahedron Lett.* **1987**, *28*, 645. (f) Drabowicz, J. *Synthesis* **1980**, 125. (g) Araujo, H. C.; Ferreira, G. A. L.; Mahajan, J. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2257. (h) Yakawa, Y.; Sakai, M.; Suzuki, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2266. (i) Erickson, R. E.; Andrulis, P. J., Jr.; Collins, J. C.; Lungle, M. L.; Mercer, G. D. *J. Org. Chem.* **1969**, *34*, 2961. (j) Bird, J. W.; Diaper, D. G. M. *Can. J. Chem.* **1969**, *47*, 145. (k) Narayanan, C. R.; Ramaswamy, O. S.; Wadia, M. S. *Chem. Ind. (London)* **1977**, 454. (l) Olah, G. A.; Ho, T. L. *Synthesis* **1976**, 610. (m) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1977**, 445. (n) Olah, G. A.; Vankar, Y. D.; Prakash, G. K. S. *Synthesis* **1979**, 113. (o) Ho, T. L. *Synth. Commun.* **1980**, *10*, 465. (p) Firouzabadi, H.; Sardarian, A. *Synth. Commun.* **1983**, *13*, 863. (q) Maeda, K.; Moritani, I.; Hosokawa, T.; Murahashi, S. I. *Tetrahedron Lett.* **1974**, 797. (r) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (s) McKillop, A.; Hunt, J. D.; Naylor, R. D.; Taylor, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 4918. (t) Butler, R. N.; Morris, G. J.; O'Donohue, A. M. *J. Chem. Res. Synop.* **1981**, *61*.

(2) (a) Alvarez, C.; Cano, A. C.; Rivera, V.; Marquez, C. *Synth. Commun.* **1987**, *17*, 279. (b) Nitta, M.; Sasaki, I.; Miyano, H.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3357. (c) Alper, H.; Edward, T. *J. Org. Chem.* **1967**, *32*, 2938. (d) Sugden, J. K. *Chem. Ind. (London)* **1972**, 680. (e) Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 195. (f) Corey, E. J.; Richman, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5276. (g) Ahmad, M. S.; Siddiqui, A. H. *J. Indian Chem. Soc.* **1969**, *46*, 44. (h) Staskun, B.; VanEs, T. *J. Chem. Soc. C* **1966**, 531.

(3) (a) Gillam, A. E.; West, T. F. *J. Chem. Soc.* **1945**, 95. (b) Hershberg, E. B. *J. Org. Chem.* **1948**, *13*, 542. (c) Chamberlin, E. M.; Chemerda, J. M. *J. Am. Chem. Soc.* **1955**, *77*, 1221. (d) Royals, E. E.; Horne, S. E., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 5856. (e) Herzog, H. L.; Payne, C. C.; Jevnik, M. A.; Gould, D.; Shapiro, E. L.; Oliveto, E. P.; Hershberg, E. B. *J. Am. Chem. Soc.* **1955**, *77*, 4781. (f) DePuy, C. H.; Ponder, B. W. *J. Am. Chem. Soc.* **1959**, *81*, 4629. (g) Cava, M. P.; Little, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257. (h) Taub, D.; Hoffsommer, R. D.; Slates, H. L.; Kuo, C. H.; Wendler, N. L. *J. Am. Chem. Soc.* **1960**, *82*, 4012. (i) Pines, S. H.; Chemerda, J. M.; Kolowski, M. A. *J. Org. Chem.* **1966**, *31*, 3446.

0022-3263/88/1953-0878$01.50/0