with HCl. Mass balance in all cases was about 90%.

Li-X and Li-Y influence the reactivity of α-alkyldeoxybenzoins in two important ways. The normal type II reactivity is suppressed in favor of the type I process. Among the type I products the abnormal product **4** is selectively formed. The important role of cation in this selectivity is obvious as the extent of selectivity decreases with Na, K, Rb, and Cs as cations, in the same order.[6] The proposed reaction sequence upon excitation of **1** in the cavities of faujasites is illustrated in Scheme II. We believe that $Li^+$ holds the included ketone in a conformation that is not favorable for γ-hydrogen abstraction.[7] (It should be mentioned, however, that such an interaction may not completely arrest the rotational and translational motions of either the ketone or the intermediates derived from it.) Therefore, the normally favored type II process is inhibited inside the cavity facilitating the occurrence of the α-cleavage. Furthermore, once the α-cleavage occurs, the translational freedom of the fragments is reduced due to their coordination to the cation as shown in Scheme II. The caged fragments recombine either with or without rearrangement; the product resulting from the former pathway alone being different from the reactant.

Support for the interaction between the cation and the ketone derives from IR and laser Raman studies[8] and earlier literature observations on related systems. The carbonyl stretching band of **1a** is shifted (1665 $cm^{-1}$) in Li-X and Li-Y with respect to that as neat (1684 $cm^{-1}$) and in dealuminated zeolite (Si/Al = 500; 1680 $cm^{-1}$). The decreased specificity with other cations is also consistent with the decrease in energy of coordination along the series $Li^+$ to $Cs^+$.[9,10] Our above proposal is consistent with the reported examples of coordination of ketones[11] and aromatics[12] to the exchangeable cations in faujasites. Additional experiments are under way to understand the mechanism of the influence of zeolite framework on this and related photoprocesses.

Near quantitative formation of a new product upon photolysis of α-alkyldeoxybenzoins in the cavities of zeolite suggests that there exists a potential for utilization of molecular sieves to alter the inherent photobehavior of organic molecules.

**Acknowledgment.** We thank A. Pittman and J. McCartney for able technical assistance and Dr. B. Chase and N. D. Rapposelli for FT IR and laser Raman spectra.

**Registry No.** **1a**, 21383-02-8; **1b**, 2371-23-5; **1c**, 38821-25-9; **1d**, 110797-71-2; **2**, 134-81-6; **3a**, 42117-21-5; **3b**, 102555-75-9; **3c**, 115756-77-9; **3d**, 115756-76-8; **4a**, 55363-57-0; **4b**, 64357-40-0; **4c**, 64357-67-1; **4d**, 115732-32-6; **5a**, 110797-72-3; **5b**, 110797-73-4; **5c**, 115732-30-4; **5d**, 115732-31-5; **6**, 451-40-1; Li, 7439-93-2; Na, 7440-23-5; K, 7440-09-7; Rb, 7440-17-7; Cs, 7440-46-2.

(6) The relative yield of **4** decreased as the cation was varied from $Li^+$ to $Cs^+$ both in X and Y type zeolites for all four ketones. For example the yield of **4** from **1a** in $M^+$-X: Na-X, 88%, K-X, 48%; Rb-X, 32%; Cs-X, 21%. Details will be presented in the full paper.

(7) It is also likely that the interaction between the cation and the carbonyl chromophore results in the weakening of the α-CC bond. This would enhance the rate of α-cleavage with respect to γ-hydrogen abstraction.

(8) Diffuse reflectance IR spectra were recorded on Nicolet FT IR spectrometer (Model 7199). The samples were heated (200 °C) under vacuum ($10^{-4}$ mm) for about 30 min prior to recording the spectrum.

(9) Preliminary TGA studies indicate that the temperature required to desorb **1a** from Li-Y, K-Y, and Cs-Y decreases in that order: Li-Y, 421 °C; K-Y, 396 °C; Cs-Y, 389 °C.

(10) It is known that the temperature required to desorb water from $M^+$-X decreases in the series Li, Na, K, Rb, and Cs as cations. Bertsch, L.; Habgood, H. W. *J. Phys. Chem.* **1963**, *67*, 1621.

(11) Geodokyan, K. T.; Kiselev, A. V.; Lygin, V. I. *Russ. J. Phys. Chem.* **1967**, *41*, 227 and 476. Bein, T.; McLain, S. L.; Corbin, D. R.; Farlee, R. F.; Moller, K.; Stucky, G. D.; Woolery, G.; Sayers, D. *J. Am. Chem. Soc.* **1988**, *110*, 1801.

(12) Newsam, J. M.; Silbernagel, B. G.; Garcia, A. R.; Hulme, R. *J. Chem. Soc., Chem. Commun.* **1987**, 664. Fitch, A. N.; Jobic, H.; Renouprez, A. *J. Chem. Soc., Chem. Commun.* **1985**, 284. Freeman, J. J.; Unland, M. L. *J. Catal.* **1978**, *54*, 183. Unland, M. L.; Freeman, J. J. *Phys. Chem.* **1976**, *82*, 1036.

**D. R. Corbin, D. F. Eaton, V. Ramamurthy***
*Central Research and Development Department*
*E. I. du Pont de Nemours and Company*
*Experimental Station*
*Wilmington, Delaware 19898*
*Received March 22, 1988*

## Use of Polar Picolyl Protecting Groups in Peptide Synthesis

*Summary:* Protection of serine and threonine side chains with the 4-picolyl group and aspartic and glutamic acids with the 3-picolyl group is described. Picolyl-protected peptide segments are markedly more polar than benzyl-protected analogues, which can facilitate their purification.

*Sir:* Despite the continuous improvement in peptide synthesis methodology, no general strategy is yet available to permit a secure synthesis of large peptides or proteins. From a synthetic point of view, it seems advisable to base any attempt to develop such an strategy on a convergent approach. Current work of this laboratory deals with the test of several methodologies to design a convergent solid-phase approach to peptide synthesis.[1] A general problem in this strategy is the unpredictable, low solubility of protected peptide segments that causes difficulties in their purification as well as in the subsequent coupling steps. This problem is even more critical in solution synthesis where peptide segments must be soluble in the appropriate solvent at every stage.[2]

It seems likely that the poor solubility of protected peptide segments is due to the contrast between the polar nature of the peptide backbone and the hydrophobicity of some amino acid side chains (e.g. Phe, Leu, Ile, Val) and common protecting groups (e.g. benzyl, benzyloxycarbonyl, *tert*-butyl, *tert*-butyloxycarbonyl (Boc)) of trifunctional amino acids. At this point, one could expect that the use of polar protecting groups would help to circumvent the problem. To achieve such polarity, protecting groups must contain an additional function free from side reactions under the conditions of the peptide synthesis strategy designed. These orthogonality requirements are very stringent and must be accompanied by deprotection methods that are clean and essentially quantitative. Altogether this makes the development of polar protecting groups for the synthesis of large-size peptides a good challenge from the point of view of organic synthesis.

Little attention has been paid to the 4-picolyl group introduced by Young et al. in 1968[3] as a "handle" to protect the C-terminal amino acid and help in the purification steps of the growing peptide chain in solution peptide

(1) (a) Pedroso, E.; Grandas, A.; Saralegui, M. A.; Giralt, E.; Granier, C.; Van Rietschoten, J. *Tetrahedron* **1982**, *38*, 1183. (b) Giralt, E.; Albericio, F.; Pedroso, E.; Granier, C.; Van Rietschoten, J. *Tetrahedron* **1982**, *38*, 1193. (c) Grandas, A.; Albericio, F.; Pedroso, E.; Giralt, E.; Sabatier, J. M.; Van Rietschoten, J. submitted for publication.

(2) (a) Finn, F. M.; Hofmann, K. *The Proteins*; Neurath, H., Hill, R. L., Eds.; Academic: New York, 1976; Vol. II, pp 105-253. (b) Kenner, G. W.; Ramage, R.; Sheppard, R. C. *Tetrahedron* **1979**, *35*, 2767.

(3) (a) Camble, R.; Garner, R.; Young, G. T. *Nature (London)* **1968**, *217*, 247. (b) Camble, R.; Garner, R.; Young, G. T. *J. Chem. Soc. C* **1969**, 1911.

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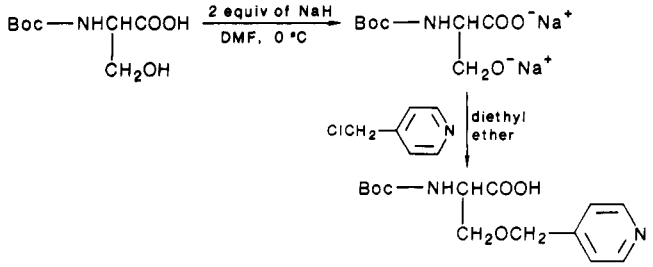
**Scheme I**




synthesis. Young has used "the picolyl ester method" extensively,[4] proving its usefulness and compatibility with general conditions used in peptide synthesis. In addition, he has described the protection of cysteine, tyrosine, and aspartic and glutamic acid side chains with the 4-picolyl group.[5] Protection of the lysine side chain with the (4-picolyloxy)carbonyl group has also been described.[6] It is likely that generalized protection with the picolyl group results in a substantial increase in solubility of protected peptide segments. With this aim, we have explored the extension of 4-picolyl protection to the alcohol side chains of serine and threonine. In addition, we have prepared $\beta$- and $\gamma$-3-picolyl esters of Boc-L-aspartic and Boc-L-glutamic acids, respectively. Having the same potential advantages, we have in this case chosen to use 3-picolyl rather than 4-picolyl protection, supposing a somewhat higher stability of 3-picolyl esters, with regard to 4-picolyl analogues, to nucleophilic attack.[7] Finally, we have studied the effect of picolyl side chain protection on the solubility properties of model protected peptide segments.

Boc-L-Ser(4-Pic)-OH has been prepared in 40% yield from Boc-L-serine by Williamson synthesis with 2 equiv of sodium hydride and 1 equiv of 4-pyridylmethyl chloride (freshly prepared from its hydrochloride)[8,9] (Scheme I): mp 143–145 °C; $[\alpha]^{20}_D$ +18.1° (*c* 1, MeOH).

The 4-picolyl ether of serine is exceptionally stable to the standard conditions of peptide synthesis.[10] No deprotection[11] has been observed in trifluoroacetic acid (TFA)–$CH_2Cl_2$, 3:7 (48 h), diisopropylethylamine (DIEA)–$CH_2Cl_2$, 1:19 (48 h), or piperidine–dimethylformamide (DMF), 1:1 (48 h). Under "high HF" (HF–anisole, 90:10) (1 h), "low HF" (HF–dimethyl sulfide–*p*-thiocresol–*p*-cresol, 25:65:5:5) (1 h), and photolysis conditions (350 nm, $CH_2Cl_2$–$CF_3CH_2OH$, 8:2) (6 h) no deprotection has been observed either.

**Table I. $C_{18}$ HPLC Retention Times of Protected Peptides I–IV[a]**

| sample | retention times, min | sample | retention times, min |
|---|---|---|---|
| I | 12.4 | III | 15.9 |
| II | 9.0 | IV | 11.2 |

[a] Linear gradient from 10% to 90% acetonitrile in 0.01 N aqueous HCl (20 min). Flow rate: 1.5 mL/min. Column: Vydac 25 × 0.4 cm, 10 $\mu$m.

Deprotection assays of the 4-picolyl ether of serine using several reductive methods have been carried out. Only partial deprotection has been attained with Zn in 80% acetic acid (4 h, 12%) and with potentiostatic electrolysis at −1.45 V in DMF–$H_2O$, 4:1, with tetraisopropylammonium perchlorate as electrolyte (4 h, 70%). Quantitative deprotection is achieved with catalytic hydrogenolysis in 80% acetic acid with 10% palladium over charcoal as catalyst (30 min) and with galvanostatic electrolysis in 0.025 M sulfuric acid at 40 mA (1 h).[12]

$\beta$- and $\gamma$-3-picolyl esters of Boc-L-aspartic and Boc-L-glutamic acids, respectively, have been synthesized, as described by Young et al. for 4-picolyl analogues,[5,13] by esterification with 2 equiv of 3-pyridylmethanol and 2 equiv of dicyclohexylcarbodiimide (DCC) in $CH_2Cl_2$ (2 h at 0 °C and 16 h at room temperature), isolation of the corresponding diester and partial saponification with 1 equiv of lithium hydroxide in acetone–$H_2O$. Isolation and crystallization gave Boc-$\beta$-3-picolyl-L-aspartic acid in 36% yield (mp 120–122 °C, $[\alpha]^{20}_D$ +1.3° (*c* 1, MeOH)) and Boc-$\gamma$-3-picolyl-L-glutamic acid in 29% yield (mp 116–118 °C, $[\alpha]^{20}_D$ −8.1° (*c* 1, MeOH)). These picolyl esters are stable to TFA–$CH_2Cl_2$, 3:7 (48 h), DIEA–$CH_2Cl_2$, 1:19 (48 h), "high and low HF" conditions (2 h), and in photolysis conditions (8 h). Piperidine–DMF, 1:1, causes slow side chain piperidineamide formation (23% in 72 h). Quantitative deprotection is done under the same conditions as 4-picolyl ethers, but in shorter times (in a few minutes).[14]

Four model protected peptides (I–IV)[15] have been synthesized on a $\alpha$-[4-(bromomethyl)-3-nitrobenzamido]-benzylcopoly(styrene-1%-divinylbenzene) resin[16] with use of Boc-amino acids (except [(fluorenylmethoxy)-carbonyl]-L-alanine (Fmoc-Ala)), DCC-mediated couplings, and photolytical cleavage from the resin. Photolysis yields ranged from 43% to 85%. No qualitative difference was observed by reverse-phase HPLC between photolysis crudes of benzyl- and picolyl-protected segments in either

(4) See, for instance, Hallett, A.; Hope, A. P.; Munns, M. S.; Richardson, R.; Young, G. T. *J. Chem. Res., Miniprint* **1983**, 501–563.

(5) (a) Garner, R.; Young, G. T. *J. Chem. Soc. C* **1971**, 50. (b) Gosden, A.; Macrae, R.; Young, G. T. *J. Chem. Res., Miniprint* **1977**, 317.

(6) Veber, D. F.; Paleveda, W. J.; Lee, Y. C.; Hirschmann, R. *J. Org. Chem.* **1977**, *42*, 3286.

(7) This is suggested by the $\sigma$ replacement substituent constants for 3-pyridyl and 4-pyridyl groups (see: Charton M. In *Correlation Analysis in Chemistry*, Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978; p 235). Some data supporting this supposition is given in ref 14. This could be important to minimize aspartimide or pyroglutamate formation in peptides containing picolyl-protected aspartyl or glutamyl residues, respectively.

(8) Attempts to carry out the reaction in the presence of $Ag^+$ ions or using potassium hydride as a base in the presence of 18-crown-6 failed to increase the yield. Use of 4-pyridylmethyl bromide, 4-pyridylmethyl tosylate, and 4-pyridylmethyl trichloroacetimidate as alkylating agents did not afford better results either. Reaction of L-serine with 4-pyridylmethanol in trifluoromethanesulfonic acid–trifluoroacetic acid, 1:19, gave no $\beta$-O-alkylated product.

(9) Application of the same procedure to the synthesis of Boc-$\beta$-4-picolyl-L-threonine gives a pure product but in a rather low yield (5%) (mp 91–92 °C, $[\alpha]^{20}_D$ +9.2° (*c* 1, MeOH)). Current utilization of this derivative would obviously imply the optimization of this synthetic method.

(10) The 4-picolyl ether of threonine exhibits the same stability.

(11) Within 0.2% error detection, by amino acid analysis.

(12) Several conditions described for the cleavage of benzyl ethers as boron trifluoride–diethyl etherate in dimethyl sulfide, potassium iodide/boron trifluoride–diethyl etherate in acetonitrile, and potassium iodide/trimethylsilyl chloride in acetonitrile failed to cleave the 4-picolyl ether of serine.

(13) Pinker, T. G.; Young, G. T.; Elliot, D. F.; Wade, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 220.

(14) In our hands, reduction with Zn in 80% acetic acid—the method of choice for 4-picolyl ester deprotection according to Young[4]—also failed here (8%, 2 h), while the $\beta$-4-picolyl ester of aspartic acid was quantitatively deprotected in 1 h under this conditions. This indicates a higher reduction potential (therefore a higher electronic density over the methylene group) for 3-picolyl esters with regard to 4-picolyl esters. This would be in accordance with a higher stability of 3-picolyl esters to nucleophilic substitution, as was pointed in the introduction. A more direct indication of this is given by the fact that Boc-$\beta$-4-picolyl-L-aspartic acid undergoes attack by piperidine (in DMF, 1:1) more rapidly (37%, 72 h) than the 3-picolyl analogue.

(15) The hexapeptide H-Pro-Pro-Gly-Phe-Ser-Pro-OH is the segment 2–7 of bradykinin. The tetrapeptide H-Ala-Gly-Asp-Val-OH has been used in a study on the effect of Arg-Gly-Asp-containing peptides on fibrinogen; see: Plow, E. F.; Perschbacher, M. D.; Ruoslahti, E.; Marguerie, G. A.; Ginsberg, M. H. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8057.

(16) Giralt, E.; Albericio, F.; Andreu, D.; Eritja, R.; Martin, P.; Pedroso, E. *An. Quim.* **1981**, *77*, 120.

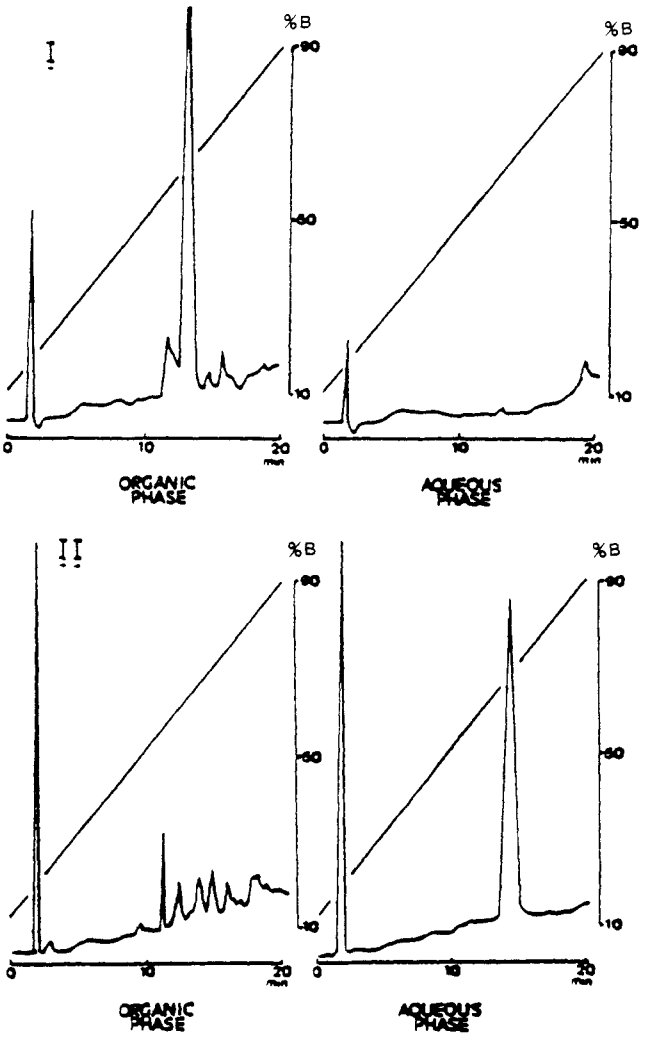



**Figure 1.** Partition experiments between ethyl acetate and 0.01 M aqueous ammonium acetate at pH 4 with protected hexapeptides I and II. Analytical HPLC on $C_{18}$ of organic and aqueous phases. Linear gradient from 10% to 90% acetonitrile (0.036% TFA) in water (0.045% TFA). Flow rate, 1.5 mL/min. Column, Spherisorb ODS-2, 30 × 0.4 cm, 10 μm; λ 220 nm.

case. The four protected peptides were purified by medium-pressure liquid chromatography on $C_{18}$.

Boc-Pro-Pro-Gly-Phe-Ser(X)-Pro-OH

I, X = Bzl

II, X = 4-Pic

Fmoc-Ala-Gly-Asp(Y)-Val-OH

III, Y = Bzl

IV, Y = 3-Pic

A first indication of the effect of picolyl protection on polarity was the lower HPLC retention times of II and IV compared to I and III, respectively, when 0.01 N aqueous HCl is used in the mobile phase (Table I). The retention times of picolyl-protected peptides (II and IV) depend markedly on the acidic component of the mobile phase, a fact that can be advantageous in selecting appropriate chromatographic conditions. Further insights of possible picolyl protection advantages were obtained in solubility experiments. The benzyl-protected hexapeptide I was partially soluble in diethyl ether while the picolyl analogue II was clearly insoluble. In partition experiments between ethyl acetate and 0.01 M aqueous ammonium acetate at pH 4, I was found quantitatively in the organic phase, as

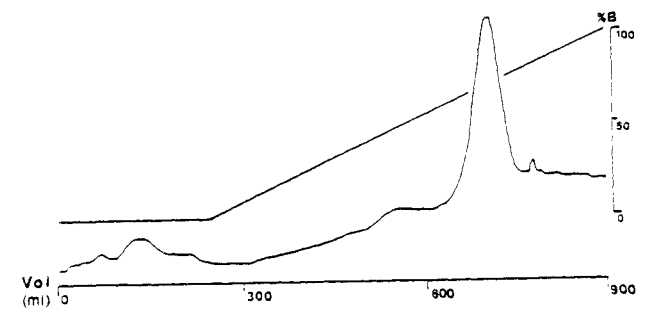



**Figure 2.** Preparative cationic exchange chromatography of IV on a column of Dowex AG WX-2 resin. (A) 0.05 M $HCOO^-NH_4^+$–dioxane, 8:2, at pH 3.0 (3.45 ms). (B) 0.3 M $HCOO^-NH_4^+$–dioxane, 6:4, at pH 4.0 (8.0 ms). Flow rate: 30 mL/h; λ 279 nm.

expected for usual protected peptides, while II was found mainly in the aqueous phase (Figure 1). The picolyl-protected tetrapeptide IV was found to be soluble in 10% acetic acid while benzyl analogue III was clearly insoluble. These experiments suggested the possibility of using cationic exchange chromatography as an alternative method to purify picolyl-protected peptides. Several preparative runs of crude protected tetrapeptide IV on (carboxymethyl)cellulose and cellulose phosphate columns, with aqueous ammonium formate and ammonium acetate buffers as eluents, were made. Selectivity was not as good as in $C_{18}$ medium-pressure chromatography due to the poor retention of the product. Although not optimum, better results were obtained by cationic exchange chromatography on sulfonated polystyrene resins (Dowex AG WX-2) adding dioxane to the mobile phase (Figure 2). To our knowledge, these are the first described examples of ionic exchange chromatography of protected peptides.

Free H-Pro-Pro-Gly-Phe-Ser-Pro-OH was obtained from I by successive treatments with TFA–$CH_2Cl_2$, 1:1 (30 min), and HF–anisole, 90:10 (1 h at 0 °C). Deprotection of II with TFA–$CH_2Cl_2$, 1:1, and subsequent hydrogenolysis in 80% acetic acid with 10% palladium over charcoal as catalyst (16 h) afforded quantitatively the free hexapeptide with comparable degree of purity (higher than 95% by HPLC). Protected tetrapeptides III and IV were fully deprotected by catalytic transfer hydrogenolysis with ammonium formate[17] in acetic acid–DMF, 1:19, with 10% palladium over charcoal as catalyst (1 h), to give H-Ala-Gly-Asp-Val-OH with purity higher than 98% in both cases.[18]

In summary, the picolyl group fulfills the requirements of an excellent semipermanent protecting group of alcohol and carboxylic acid side chains in a convergent solid-phase approach to peptide synthesis. It is expected that it can also be advantageously used in solution peptide synthesis. Use of only one picolyl side chain protecting group has proved to induce pronounced differences in solubility of protected peptide segments. This can be of great advantage in protected peptide segments purification, avoiding the use of DMF in reversed-phase medium-pressure chromatography (which precludes low wavelength detec-

(17) (a) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929. (b) Anwer, M. K.; Spatola, A. F.; Bossinger, C. D.; Flanigan, E.; Liu, R. C.; Olsen, D. B.; Stevenson, D. *J. Org. Chem.* **1983**, *48*, 3503.

(18) A little amount of acetic acid is convenient to prevent aspartimide formation during hydrogenolysis. See: Perseo, G.; Forino, R.; Galantino, M.; Gioia, B.; Malatesta, V.; de Castiglione, R. *Int. J. Peptide Protein Res.* **1986**, 51. Both benzyl and 3-picolyl protecting groups are cleaved in about 3 min. The hydrogenolysis was prolonged to fully eliminate the Fmoc protection. Hydrogenolysis of the Fmoc group has been described earlier. See, for instance: Martinez, J.; Tolle, J. C.; Bodanzsky, M. *J. Org. Chem.* **1979**, *44*, 3596.

tion) and opening the possibility of alternative purification methods such as cationic exchange chromatography.

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**Registry No.** I, 116596-44-2; II, 116633-81-9; III, 116596-45-3; IV, 116596-46-4; BOC-Ser-OH, 3262-72-4; BOC-Thr-OH, 2592-18-9; (4-Pic)Cl, 10445-91-7; BOC-Ser(4-Pic)-OH, 116596-36-2; BOC-Thr(4-Pic)–OH, 116633-80-8; H-Ser(4-Pic)-OH, 116596-37-3; H-Ser-OH, 56-45-1; BOC-Asp-OH, 13726-67-5; BOC-Glu-OH, 2419-94-5; (3-Pic)OH, 100-55-0; BOC-Asp(O(3-Pic))-O(3-PIc), 116596-38-4; BOC-Glu(O(3-Pic))-O(3-Pic), 116596-39-5; BOC-Asp(O(3-Pic))-OH, 116596-40-8; Boc-Glu(O(3-Pic))-OH, 116596-41-9; BOC-Asp(1-piperidinyl)-OH, 116596-42-0; BOC-Glu(1-piperidinyl)-OH, 116596-43-1; BOC-Ser(Bzl)-OH, 23680-31-1; BOC-Asp(OBzl)-OH, 7536-58-5; BOC-Pro-OH, 15761-39-4; BOC-Gly-OH, 4530-20-5; BOC-Phe-OH, 13734-34-4; BOC-Val-OH, 13734-41-3; Fmoc-Ala-OH, 35661-39-3; H-Pro-Pro-Gly-Phe-Ser-Pro-OH, 23828-06-0; H-Ala-Gly-Asp-Val-OH, 99896-90-9; H-Asp-OH, 56-84-8; H-Glu-OH, 56-86-0; $(i\text{-Pr})_4N^+ \cdot ClO_4^-$, 116596-47-5.

**Josep Rizo,† Fernando Albericio,† Guillermo Romero† Carlos García-Echeverría,† Josep Claret‡ Carlos Muller,‡ Ernest Giralt,† Enrique Pedroso*,†**

*Departments of Organic and Physical Chemistry University of Barcelona 08028 Barcelona, Spain*

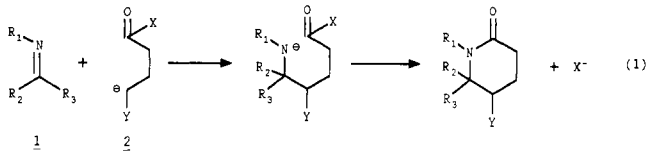
*Received May 12, 1988*

†Department of Organic Chemistry.
‡Department of Physical Chemistry.

## Remote Dianions. 3. Novel Synthesis of Substituted 2-Piperidones from Imines[1]

*Summary:* The dianion of 4-(phenylsulfonyl)butanoic acid reacts with imines activated by boron trifluoride etherate to afford, after cyclization, substituted 2-piperidones.

*Sir:* Imines have been relatively under utilized (yet easily prepared[2]) functional groups in the synthesis of heterocycles. Recently, certain derivatives of imines have been employed in cycloaddition chemistry,[3] and addition reactions to the imine moiety have been reported[4] (primarily via activation with Lewis acids), opening new opportunities for the construction of aza heterocyclic compounds. Indeed, an intramolecular extension of this latter process seemed particularly attractive to us since the second linkage, subsequent to addition of a nucleophile, could be formed by dehydration or acylation (eq 1; X = OR, OH, etc.).



1 2 (1)

Previously, we reported that the dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA) (**2**; X = $O^-$, Y = $PhSO_2$) reacts readily with a variety of carbonyl compounds to afford, after tandem cyclization assisted by trifluoroacetic anhydride (TFAA), pentanolides in good yield.[5] Application of this method to imines should provide rapid entry to the analogous nitrogen compounds (2-piperidones), assuming addition to the imine is successful. These derivatives would be of wide general interest owing to the number of piperidine natural products.[6] We now report that the reaction of imines activated with $BF_3 \cdot Et_2O$[7] with 4-PSBA dianion leads to 2-piperidones in high yields in a simple, one-pot process (eq 2, Table I).

In a general procedure, the dianion of 4-PSBA (THF; 4.25 mmol, 0.075 M) was generated as previously described.[5] The dianion was maintained at −78 °C while in a separate flask the imine (4 mmol) was dissolved in 7 mL of THF and chilled to −78 °C. $BF_3 \cdot Et_2O$ (4 mmol) was added to the imine solution, occasionally giving a milky suspension (depending on imine). The activated imine was added to the yellow dianion solution via cannula or syringe. After the addition was complete, the mixture generally became colorless. The mixture was allowed to stir at −78 °C for 0.5 h to complete the addition. Then TFAA (8 mmol) was added at −78 °C, the cold bath was removed, and the mixture was stirred an additional 0.5 h. The reaction was diluted with an equal volume of diethyl ether and poured into saturated bicarbonate. Isolation of the crude product by crystallization ($CHCl_3/Et_2O$) or flash chromatography (100% ether) gave pure lactam.[8] The results of this sequence are presented in Table I.

It is evident that both aldimines and ketimines are amenable to addition–cyclization with 4-PSBA. Entry **3e**, which involved addition to the benzyl imine of cyclohexanone, is of particular interest since the 1-azaspiro[5.5]undecan-2-one, a model for histrionicotoxin and congeners,[9] is formed in good yield from inexpensive materials.

To extend the utility of this method would require effective desulfonylation of the intermediates **3a–f**.[10] At

(1) (a) Part 2 see: Thompson, C. M.; Frick, J. A.; Woytowicz, C. E. *Synth. Commun.* **1988**, *18*, 889. (b) Presented in part at the *12th Mona Symposium of Natural Products and Medicinal Chemistry*; Mona, Jamaica, January 1988.

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