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NITROGEN ALKYLATION OF SCHIFF BASES AND AMIDINES AS A ROUTE TO N-ALKYL AMINO ACIDS[1]

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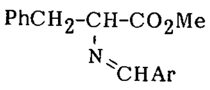
Abstract: Schiff base and amidine esters 3 are alkylated and then hydrolyzed to yield N-alkyl amino acids 4 in 41-75% yield with high to complete retention of optical activity.

The utilization of natural as well as unnatural amino acids continues to grow in practically all areas of the physical and life sciences. N-alkyl amino acids are an important class of amino acids: as biologically active species,[2] in the preparation of peptide analogs[3] and in conformational studies of peptides.[4] The major method for the preparation of the N-alkyl amino acids involves alkylation (NaH, RX) of a suitably protected amino nitrogen (t-butyloxcarbonyl, Boc, or benzyloxycarbonyl, Cbz).[5] Several other methods of interest have been reported recently.[6]

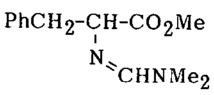
We would like to report our preliminary findings on an alternate route to N-alkyl amino acids which involves nitrogen alkylation of imine-type derivatives with electrophiles. This procedure is analogous to the Decker reaction[7] for conversion of a primary into a secondary amine by alkylation of the in-situ generated Schiff base followed by hydrolysis of the resulting iminium salt.

Two model systems derived from phenylalanine, the Schiff bases 1 and the amidine esters 2 were chosen for initial experiments. Compounds 1[8] were expected to be somewhat less reactive than the imines



$\mathrm{PhCH_2\text{-}CH(N{=}CHAr)\text{-}CO_2Me}$

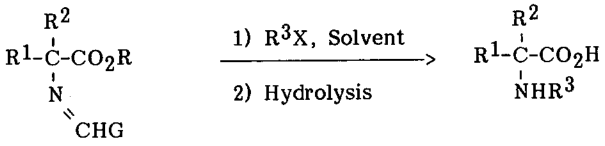
1



$\mathrm{PhCH_2\text{-}CH(N{=}CHNMe_2)\text{-}CO_2Me}$

2

TABLE. Preparation of N-Alkyl Amino Acids.



$$R^1\text{-}\overset{R^2}{\underset{N{=}CHG}{C}}\text{-}CO_2R \xrightarrow[\text{2) Hydrolysis}]{\text{1) }R^3X\text{, Solvent}} R^1\text{-}\overset{R^2}{\underset{NHR^3}{C}}\text{-}CO_2H$$

3 4

Entry	Compd	R^1	R^2	G	R	R^3X	Method[a]	%4[b]	$[\alpha]_D^T$
1	L-4a	$PhCH_2$	H	$4\text{-}ClC_6H_4$	Me	Me_2SO_4	A	61%	+17.4° (c)
2	DL-4a	$PhCH_2$	H	$4\text{-}MeOC_6H_4$	Me	Me_2SO_4	A	56%	d
3	L-4a	$PhCH_2$	H	$4\text{-}ClC_6H_4$	Me	MeOTf	B	73%	+18.9° (c)
4	L-4a	$PhCH_2$	H	Me_2N	Me	Me_2SO_4	See Text	73%	+1.9° (c)
5	L-4a	$PhCH_2$	H	Me_2N	Me	Me_2SO_4	C	58%	+19.6° (c)
6	L-4a	$PhCH_2$	H	Me_2N	Et	MeOTf	B	41%	+19.4° (c)
7	DL-4b	$PhCH_2$	H	Me_2N	Me	Et_2SO_4	C	64%	d
8	L-4c	iPr	H	Me_2N	Me	Me_2SO_4	C	48%	+30.6° (e)
9	DL-4d	$ArCH_2$[f]	H	Me_2N	Me	Me_2SO_4	C	63%	d
10	DL-4e	nC_8H_{17}	H	Me_2N	Me	Me_2SO_4	C	75%	d
11	DL-4f	$ArCH_2$[f]	CH_3	Me_2N	Me	Me_2SO_4	C	63%	d
12	D-4g	Ph	H	Me_2N	Me	Me_2SO_4	C	58%	-16.0° (g)
13	D-4g	Ph	H	Me_2N	Me	MeOTf	D	64%	-168.4° (g)
14	L-4g	Ph	H	Me_2N	Me	MeOTf	D	59%	+166.0° (g)

[a] Method A: $PhCH_3$, reflux, 24 h.; Method B: CH_2Cl_2, 25°C, 12-16 hr.; Method C: $PhCH_3$, reflux, 1 hr.; Method D: CH_2Cl_2, 25°C, 1 hr.

[b] Isolated N-alkyl amino acid, not optimized. All new compounds gave elemental analyses and proton NMR spectra consistent with the assigned structures.

[c] T = 25°C, c = 1, 1N HCl; $[\alpha]_D^{25}$ = +20.6° for commercial sample of N-MePhe (US Biochemical).

[d] Racemic starting material used.

[e] T = 17°C, c = 1.4, 5N HCl; Lit. $[\alpha]_D^{17}$ = +30.0° (c = 1.4, 5N HCl), Ref. 14.

[f] $ArCH_2$ = $4\text{-}ClC_6H_4CH_2$.

[g] T = 28°C, c = 2.0, 5N HCl; Lit. $[\alpha]_D^{28}$ = -159.5° (c = 2.0, 5N HCl), Ref. 15.

derived from alkyl amines because of the electron-withdrawing ester group. On the other hand, amidines 2[9] should be more reactive than 1 since amidines are considerably more basic than Schiff bases.[10] Indeed, initial experiments with alkylation of 1 (Ar = 4-ClC_6H_4) under typical Decker conditions (Me_2SO_4, $PhCH_3$, reflux, one hour) yielded recovered starting material whereas a 58% overall yield of N-methylphenylalanine was obtained by alkylation of the amidine 2 followed by hydrolysis (Table, entry 5). The Schiff bases 1 can be successfully alkylated either by increasing the reaction time (entries 1 and 2) or by using a more reactive electrophile such as methyl trifluoromethanesulfonate[11] (MeOTf) (entry 3). Two reactions of note are the preparation of N-ethylphenylalanine (entry 7) and the N-methylation of a sterically demanding α-methyl amino acid derivative (entry 11).

The effect of the type of starting substrate as well as the reaction conditions on the extent of racemization of an optically active amino acid derivative are illustrated in the Table. In general, better results are obtained by using the more reactive amidines with either dimethyl sulfate and short reaction times in refluxing toluene (entries 5 and 8) or with methyl triflate in methylene chloride at room temperature (entry 6). Although the reported one-pot procedure for the preparation of amidine esters such as 2 (amino acid, excess dimethylformamide dimethylacetal, reflux)[9] is convenient, it results in nearly complete loss of stereochemical integrity when an optically active amino acid is used (entry 4). This problem is overcome by initial preparation of the amino ester followed by reaction with dimethylformamide dimethylacetal under mild conditions. The resulting amidine ester is then alkylated immediately. Such a procedure avoids high temperature and long reaction times under which the basic amidines can racemize.

Phenylglycine is known to undergo racemization readily because of the electron-withdrawing phenyl group attached directly to the α-carbon[12] and should, therefore, provide a rigorous test for racemization with any N-methylation procedure. While methylation with dimethyl sulfate results in extensive racemization (entry 12), the use of methyl triflate with the amidine in methylene chloride at room temperature (entries 13 and 14) results in high to complete retention of configuration in the product, N-methyl phenylglycine[13] and, therefore, represents the best conditions for the preparation of N-methyl amino acids using this method.

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References and Notes

1. Presented in part at the 185th ACS National Meeting, Seattle, WA, March 25, 1983, ORGN 257.
2. J.D. Kemp, "Mol. Biol. Plant Tumors", G. Kahl and J.S. Schell, Eds.; Academic Press, New York, 1982, p. 461.
3. D.M. Zimmerman and P.D. Gesellchen, Ann. Rep. Med. Chem., 17, 21 (1982).
4. a) H. Kessler, Angew. Chem., Int. Ed. Engl., 21, 512 (1982); b) M.K. Dhaon and R.K. Olsen, J. Org. Chem., 46, 3436 (1981).
5. a) J.R. Coggins and N.L. Benoiton, Can. J. Chem., 49, 1968 (1971); b) S.T. Cheung and N.L. Benoiton, ibid, 55, 906 (1977); c) R.T. Shuman, E.L. Smithwick, D.L. Smiley, G.S. Brooke and P.D. Gesellchen, Peptides: Structure and Function, Proc. 8th Amer. Pept. Symp., 143 (1983).
6. a) R.M. Freidinger, J.S. Hinkle, D.S. Perlow and B.H. Arison, J. Org. Chem., 48, 77 (1983); b) F. Effenberger, U. Burkard and J. Willfahrt, Angew. Chem., Int. Ed. Engl., 22, 65 (1983).
7. a) H. Decker and P. Becker, Ann., 395, 362 (1913); b) A. Brossi and B. Pecherer in "Chemistry of the Alkaloids," S.W. Pelletier, Ed., Van Nostrand, N.Y., 1970, Chapter 2.
8. L. Ghosez, J.P. Antoine, E. Deffense, M. Nivarro, V. Libert, M.J. O'Donnell, W.A. Bruder, K. Willey and K. Wojciechowski, Tetrahedron Lett., 23, 4255 (1982).
9. J.J. Fitt and H.W. Gschwend, J. Org. Chem., 42, 2639 (1977).
10. The pKa of the conjugate acid of diphenylketimine ($\mathrm{Ph_2C{=}NH}$) is 7.2 while that of benzamidine ($\mathrm{Ph(H_2N)C{=}NH}$) is 11.2. See: a) J.W. Smith in "The Chemistry of the Carbon-Nitrogen Double Bond," S. Patai, Ed., Interscience, 1970, p. 237 and b) G. Hafelinger in "The Chemistry of Amidines and Imidates," S. Patai, Ed., Interscience, 1975, p. 14.
11. P.J. Stang, M. Hanack and L.R. Subramanian, Synthesis, 85 (1982).
12. a) G.G. Smith and T. Sivakua, J. Org. Chem., 48, 627 (1983); b) R. Grigg and H.Q.N. Gunaratne, Tetrahedron Lett., 24, 4457 (1983).
13. Typical procedure (Table, entry 13): anhydrous ammonia was bubbled (1 hr) with stirring into a flask containing D-phenylglycine methyl ester hydrochloride (2.02 g, 10 mmol) and ether (60 ml). The mixture was filtered to remove ammonium chloride and the solvent evaporated. Methylene chloride (60 ml) and N,N-dimethylformamide dimethylacetal (1.79 g, 15 mmol) were added and the mixture was stirred overnight at room temperature. The solvent was evaporated to give 2.11 g of crude amidine which was used directly in the next step. Methyl triflate (2.46 g, 15 mmol) was added in one portion to the above crude product in methylene chloride (50 ml) and the resulting solution was stirred at room temperature for one hour. The organic solvent was evaporated, concentrated hydrochloric acid (20 ml) was added and the solution was refluxed for one hour. After cooling to room temperature, the reaction mixture was extracted with ether (3 x 50 ml). Ion-exchange resin (IR-120$^+$, 50 ml) and water were added to the aqueous layer, the mixture was stirred overnight, the resin was filtered and washed with water until the filtrate showed a negative test for chloride ion ($\mathrm{AgNO_3}$, EtOH). The resin was combined with 6N ammonium hydroxide (150 ml) and stirred overnight. Filtration and evaporation of water followed by washes with water, methanol and ether gave 1.06 g (64%) of N-methyl phenylglycine.
14. P.A. Plattner and U. Nager, Helv. Chim. Acta, 31, 665 (1948).
15. G. LiBassi, P. Ventura, R. Monguzzi and G. Pifferi, Gazz. Chim. Ital., 107, 253 (1977).

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