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PREPARATION OF (±)-α-ALKYLATED AMINO ACID DERIVATIVES VIA IMIDAZOLES‡

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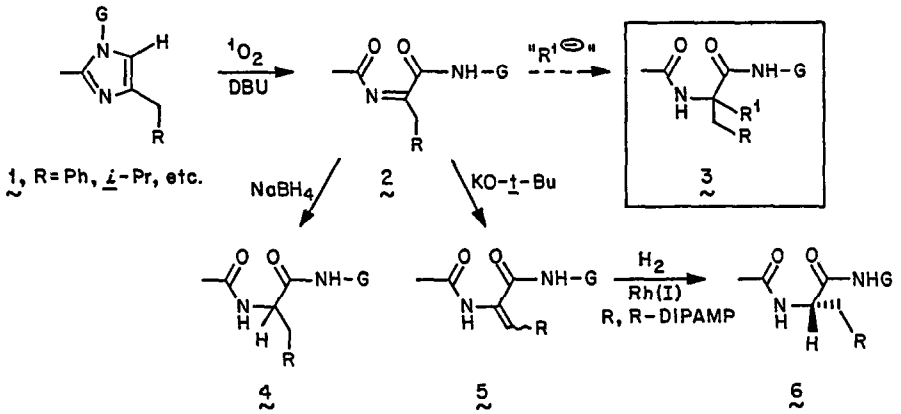
Abstract: Photooxidation of N-methoxy-2,4-disubstituted imidazoles, readily available by way of a three component cyclization followed by O-alkylation, leads to stable acyl imines which react with various organometallics to afford α,α-disubstituted amino acid bis-amides in good yields.

In an earlier communication[2] from these laboratories a method was described for converting 1,2,4-trisubstituted imidazoles 1 to amino acid bis-amides (i.e., 4). Treatment of variously derivatized systems 1 with singlet oxygen, followed by base-induced isomerization of the initial photoadducts 2 with KO-t-Bu, gives dehydroamino acid derivatives 5. These hydrogenate nicely under the influence of a chiral catalyst to amino acid bis-amides 6 of high ee's. Also noted with great interest was the finding that acyl imines 2 cleanly and regiospecifically

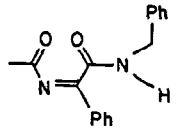


react with $NaBH_4$ to give the racemic versions of 6 (i.e., 4). The electrophilicity of these imines, coupled with their ease of preparation and stability towards isolation, suggested that carbon nucleophiles might add as well, thereby leading to several novel α-alkylated amino acids in their bis-amide forms. Incorporation of such modified, highly sought[3] amino acids into certain peptides impart valuable bioactivity profiles, including enzyme inhibiting prop-

‡Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

erties.[4] We now report that, given the approriate substitution pattern on the heteroaromatic imidazole ring, compounds of type 3 can easily be realized which incorporate functional groups R′ not readily arrived at by any of the known literature procedures.[3]

Using the latent phenylglycine system 7 as a test case, numerous reagents were investigated including RLi, RMgX, $R_2Cu(CN)Li_2$,[5] $RLi \cdot CeCl_3$,[6] and R_3ZnLi.[7] In not one case was any of the anticipated product observed. Modifications in solvent (THF, Et_2O, CH_2Cl_2), temperatures (-78 → rt), and equivalents of reagent (1-5 equiv) did not alter the outcome in a positive way. To insure that the problem was not due to the acidity of the amide NH, 7 was methylated (NaH/MeI) to afford 8, however, as before, there was no change in reaction course.



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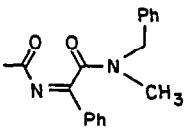

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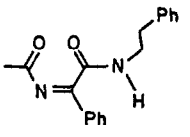

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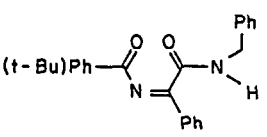

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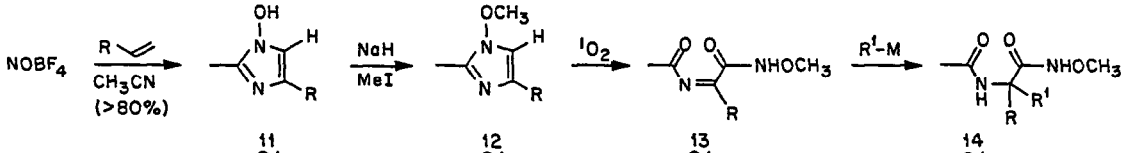
Even experiments on substrates having alterations at both nitrogen (i.e., 9; from benzyl to phenethyl) and C-2 (i.e., 10; from methyl to phenyl or t-Bu which likewise removes potentially acidic protons), met with total failure.

In reviewing these results, one last opportunity presented itself by virtue of the route developed for arriving at imidazoles 1. That is, as heterocycles 1 are formed via the corresponding N-hydroxyimidazoles (derived from $CH_3CN/NOBF_4$ + a terminal olefin in >80% yields)[8] followed by $TiCl_3$-mediated N-O cleavage[9] and N-alkylation,[8] it occurred to us that O-alkylation of 11 might ultimately afford hydroxamic derivatives 13 as compared with amides 7. Hence, treatment of 11 with NaH/MeI leads to 12, which reacts with $^1O_2$ at even a greater rate than do imidazoles 1 to afford imines 13 (>90%, isolated). Remarkably, upon exposure of

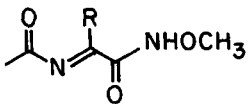
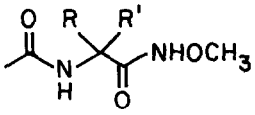


these new acyl imines to the same organometallic reagents cited earlier, we found that ALL reacted smoothly and quickly (<30 min) at 0 - -78°C[10] in good to excellent yields![11]

Table I summarizes our observations, about which some key points should be made: (1) the easiest procedure[10] calls for the use of either RLi or RMgX; (2) 2.2-2.5 equivalents of nucleophile are needed for optimum results; use of 1 equiv MeLi followed by another RLi gives bad mixtures, while employment of 1 equiv LDA and thence RLi results in ca. 20% lower yields; (3) primary, secondary, vinyl, aryl, and acetylenic groups may all be introduced in a very straightforward manner.

In summary, the concept of heteroaromatics as latent functionality has been demonstrated,[12] in this case utilizing an imidazole as a masked peptide equivalent. The short sequence delineated (i.e., 11 → 12 → 13 → 14) involves the coupling of a carbon nucleophile with an electrophilic amino acid component. This procedure represents a rare example of such an

Table I. Addition of Organometallic Reagents to Acyl Imines 13

Imine 	Organometallic (equiv)		Product (s)[a] 	Yield (%)[b]
R = n-Bu	PhLi	(2.5)	R' = Ph	87
	s-BuLi	(2.5)	R' = s-Bu	78
		(2.5)	R' = vinyl	78
		(2.5)	R' = vinyl	53
R = Ph	$Me_2Cu(CN)Li_2$	(2.5)	R' = Me	71
	n-$Bu_2Cu(CN)Li_2$	(2.5)	R' = n-Bu	75
	s-$Bu_2Cu(CN)Li_2$	(2.5)	R' = s-Bu	57
		(2.2)	R' = vinyl	72
		(2.5)	R' = vinyl	94
	PhLi	(2.5)	R' = Ph	82
	n-BuLi	(1.8)	R' = n-Bu	86
	s-BuLi	(2.5)	R' = s-Bu	61
	$LiEt_3BD$	(2.5)	R' = D	87
R = i-Bu	n-BuLi · $CeCl_3$	(2.4)	R' = n-Bu	75
	PhLi	(2.5)	R' = Ph	77
		(2.2)	R' = vinyl	52
	TMS−≡−Li	(2.5)	R' = TMS−≡−?	56
		(2.5)	R' = vinyl	61
	n-BuLi	(1.1)	R' = n-Bu	66

[a] All products gave satisfactory IR, NMR, MS, and HRMS data. [b] Isolated, pure materials via recrystallization and/or column chromatography.

umpolung for arriving at α,α-carbon disubstituted systems.[13] The ability to introduce groups irrespective of hybridization adds tremendous flexibility to this scheme, not possible in a direct way using metalated amino acid equivalents[3] and, e.g., vinyl or aryl halides as reaction partners. Further studies aimed at controlling the facial delivery of a carbon nucleophile to a chiral analog (i.e., 2, G = a chiral auxiliary) are presently in progress.

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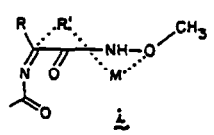
8. Lipshutz, B.H., Morey, M.C., J. Org. Chem., 1983, 43, 3745; more recently, we find that addition of the olefin in CH_3CN via a syringe pump to a solution of $NOBF_4/CH_3CN$ at -30°C affords excellent yields of N-hydroxyimidazoles; unpublished observations of W. Vaccaro and B. Huff.
9. Lipshutz, B.H., Morey, M.C., Tetrahedron Lett., 1984, 25, 1319.
10. Typical procedure: imine 13 (R = n-Bu, 63.7 mg, 0.32 mmol) was placed in a 15 mL 2-necked flask and dried azeotropically (toluene 2x5mL) and then filled with Ar. THF (3.0 mL) was added and the solution cooled to -78°C. Phenyllithium (0.38 mL, 0.80 mmol, 2.12 M) was then introduced and the mixture was stirred for 30 min at -78°C. Quenching with 1 mL of saturated NH_4Cl/1 mL brine and extractive workup with CH_2Cl_2 after initial removal of the organic layer gave the crude product. Purification on SiO_2 with 55/45/5 CH_2Cl_2/EtOAc/MeOH gave 56.3 mg (86%) product; IR ($CHCl_3$) cm^{-1} 3020, 1677, 1216, 1046, 767; NMR ($CDCl_3$) δ 8.62 (1H, bs), 7.34 (5H, m), 6.98 (1H, bs), 3.65 (3H, s), 2.02 (3H, s), 1.30 (6H, m), 0.90 (3H, t, J=7Hz); MS (CI) m/e (rel. int.) 279 ($M^+ + 1$, 2.8), 232(47), 204(100), 162(56), 104(16); HRMS (CI) calcd 279.1708; found 279.1716.
11. Why the hydroxamic acid derivative 13 reacts with numerous R-M, whereas imines 2 (G = CH_2R") and 7-10 are inert, is unclear. We speculate that the oxygen provides a critical site of complexation for R-M such that an intermediate/transition state of type i may be formed which positions R for delivery to the imine center.



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12. For a review, see Lipshutz, B.H., Chemical Reviews, in press.
13. See also, Ozaki, Y., Iwasaki, T., Horikawa, H., Miyoshi, M., Matsumoto, K., J. Org. Chem., 1979, 44, 391. Related reports on electrophilic amino acid synthons for arriving at either α-substituted or α-heteroatom-α-carbon disubstituted systems include: Sinclair, P.J., Zhai, D., Reibenspies, J., Williams, R.M., J. Am. Chem. Soc., 1986, 108, 1103; O'Donnell, M.J., Bennett, W.D., Polt, R.L., Tetrahedron Lett., 1985, 26, 695; O'Donnell, M.J., Falmagne, J.-B., ibid., 1985, 26, 699; Kober, R., Papadopoulos, K., Miltz, W., Enders, D., Steglich, W., Tetrahedron, 1985, 41, 1693; Schollkopf, U., Neubauer, H.J., Hauptrief, M., Angew. Chem. Int. Ed. Engl., 1985, 24, 1066; Shono, T., Matsumura, Y., Inoue, K., J. Org. Chem., 1983, 48, 1388; Herscheid, J.D.M., Nivard, R.J.F., Tijhuis, M.W., Scholten, H.P.H., Ottenheijm, H.C.J., ibid., 1980, 45, 1880.

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