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THE SYNTHESIS OF AMINO ACIDS BY REACTION OF AN ELECTROPHILIC GLYCINE CATION EQUIVALENT WITH CARBON NUCLEOPHILES

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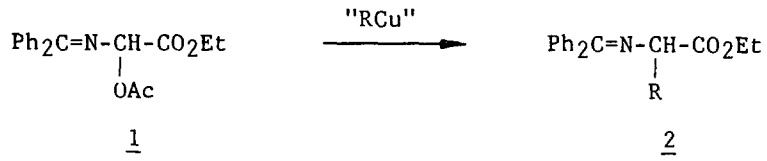
Abstract: Acetate **1**, a glycine cation equivalent, is reacted with organocopper reagents to yield products **2** which can readily be converted to the higher amino acids. This method provides access to aryl-substituted amino acids as well as amino acids containing a β-tertiary carbon.

The preceeding paper[1] outlines the preparation of a stable cationic glycine equivalent which can be reacted with heteroatom-nucleophiles to yield a variety of α-heteroatom substituted amino acid derivatives. We now report use of this synthon for the construction of carbon-carbon bonds. Of particular note is the possibility of using such a system for direct access to various structural types of amino acids which are difficult to prepare using a strategy involving reaction of a nucleophilic amino acid synthon with electrophiles. Aryl amino acids[2] as well as amino acids containing a β-tertiary carbon center[3] are two such examples.

The possibility of using organocopper reagents as the nucleophile was pursued because of the potential for a wide range of both reactivity and selectivity.[4] The multifunctional nature of the electrophilic acetate **1** makes it imperative that a selective nucleophilic reagent be chosen for introduction of the new carbon-carbon bond into the desired α-position.

Initial experiments (Table, entries 1-8) led to the choice of the higher order mixed cuprates ($R_2Cu(CN)Li_2$) developed by Lipshutz and coworkers[6] as

TABLE. Preparation of Higher Amino Acid Derivatives from Acetate 4.



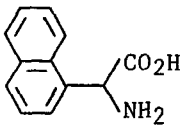
1 2

Entry	Organocopper[a]	Conditions[b]	Product[c]	Yield[d]
1	$Ph_2CuLi \cdot P(OEt)_3$[5]	THF, 0°C, 1hr, N	2a	40%
2	$Ph_2Cu(CN)Li_2$[6]	THF, -60°C, 0.5hr, N	No Rx	-
3		THF, -20°C, 1.5hr, N	No Rx	-
4		THF, 0°C, 2hr, N	2a + Redn	56%[e]
5		Et_2O, ≤-5°C, 2hr, N	Redn	70%
6		THF, ≤-5°C, 4hr, I	2a	68%
7	$Bu_2Cu(CN)Li_2$	THF, ≤-5°C, 2hr, I	2b	46%
8	$BuCu(NCy_2)Li$[7]	THF, 0°C, 2hr, N	2b	46%
9	$(1\text{-Npth})_2Cu(CN)Li_2$[8]	THF, ≤-5°C, 2hr, I	2c	63%
10	$(2\text{-Thi})_2Cu(CN)Li_2$[9]	THF, ≤-5°C, 6hr, I	2d	71%[f]
11	$(tBu)_2CuCNLi_2$	THF, ≤-5°C, 4hr, I	2e	54%

a 1.2 eq for entries 1-5 and 8; 1.5 eq for entries 6,7 and 9-11. 1-Npth = 1-Naphthyl-, 2-Thi = 2-thienyl-.
b Solvent, temperature, time and mode of addition (N = normal, I = inverse).
c Redn = reduction product (2, R = H).
d Isolated yield of 2. All products gave satisfactory elemental analyses and NMR spectra in agreement with the assigned structure.
e HPLC yield of 2a.
f See footnote 9 for a typical procedure.

reagents for the selective introduction of the requisite carbon-carbon bond. These results show that the reaction is sensitive to temperature, solvent and mode of addition. Thus, in THF with normal addition, when the temperature is too low (entries 2 and 3) no reaction occurs, whereas, at higher temperature (0°C., entry 4), significant amounts of reduction product (2, R = H) are observed. Reduction becomes the exclusive mode of reaction when ether is used as solvent (entry 5).[11] Comparison of the $nBu_2Cu(CN)Li_2$ reagent (entry 7) with another stable organocopper species, the heterocuprate $nBuCu(NCy_2)Li$[7] (entry 8) gave identical results. Using the best conditions with the higher order mixed cuprates (entry 6: inverse addition of the organocuprate to acetate 1 in THF at ≤-5°C.), several alkylated Schiff bases 2 were prepared in moderate to good yield (entries 6,7,9-11).

The alkylated Schiff bases 2 can readily by hydrolyzed to the corresponding amino acids.[12] Thus, the following amino acids were prepared (Schiff base,



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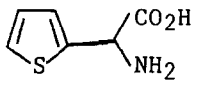

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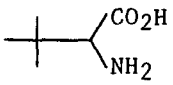

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hydrolysis yield, overall yield from 1): D,L-phenylglycine[13] (2a, 98%, 67%); D,L-norleucine[14] (2b, 80%, 37%); D,L-(1-naphthyl)glycine[15], 3 (2c, 66%, 42%); D,L-(2-thienyl)glycine[16], 4 (2d, 84%, 60%); and tert-leucine[17] 5 (2e, 90%, 49%).

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9. Typical procedure (Table, Entry 10): 2-thienyl lithium was prepared by adding nBuLi (5 ml, 2.4 M, 12 mmol) to thiophene (1.1 g, 13 mmol) in ether (5 ml) at 20 °C. (footnote 10) and was transferred by double-tipped needle to another flask containing a mixture of dry CuCN (540 mg,6 mmol, azeotroped with toluene (6 ml) under vacuum) and THF (10 ml) at -78 °C. The mixture was warmed to 0 °C. and after 2-5 min further the solution was transferred to a dropping funnel at -60 °C. and then added dropwise over 30 minutes to a solution of acetate 1 (1.3 g, 4 mmol) in THF (60 ml) at -10° to -5°C. The resulting mixture was stirred for six hours at ≤ -5 °C (disappearance of 1 was followed by HPLC). The mixture was quenched at 0 °C. with saturated NH_4Cl, brought to pH 7-8 with 6N NH_4OH, extracted with ether and the ether extracts dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (Et_2O/ hexane, 15/85) to give 2d (1.0 g, 71%). Crystallization with ether-hexane gave analytically pure product, mp 85-6 C., NMR ($CDCl_3$) δ 1.23 (3H, t), 4.16 (2H, q), 6.9-7.9 (13H, m). Anal. Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.36; H, 5.34; N, 3.96.
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14. D,L-Norleucine, mp 282-4 °C. (commercial sample, Aldrich Chemical Co., mixed mp 284-6 °C.).
15. Methyl D,L-(1-naphthyl)glycine hydrochloride (3 + MeOH/HCl), mp 176-8 °C. (Lit. mp 177-8.5 °C., H.E. Baumgarten, S.E. Dirks, J.M. Peterson and R.L. Zey, J. Org. Chem, 31, 3708 (1966)).
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17. D,L-tert-Leucine, mp 248-9 °C. (commercial sample, Research Organics, Inc., mixed mp 248-50 °C.).

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