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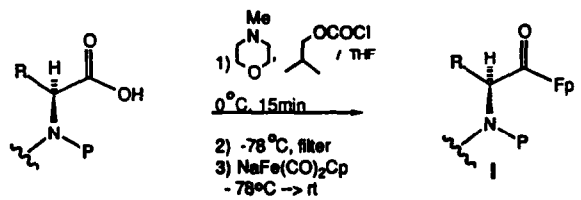
CONVENIENT SYNTHESIS OF OPTICALLY ACTIVE IRON ACYLS

R. W. Hungate*, F. Miller and M. S. Goodman
Department of Chemistry
Arizona State University
Tempe, AZ 85287-1604

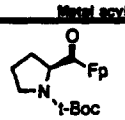
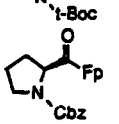
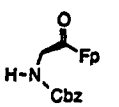
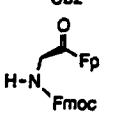
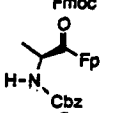
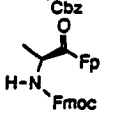
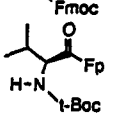
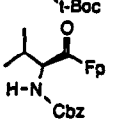
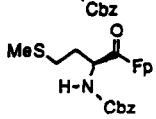
Summary: The synthesis of iron acyls derived from $Cp(CO)_2FeNa$ which incorporate optically active α amino acids is described.

Transition metal acyls have received considerable attention recently and in spite of this activity, there appears to be no report where an optically active α-amino acid is incorporated as the acyl portion.[1] We have initiated studies to examine the synthesis and reactions of protected amino acids covalently attached to transition metals and as optically active precursors for α-hydroxy β-amino acids.[2] Initially, we have concentrated on the readily available organometallic anion, $Cp(CO)_2FeNa$,[3] in anticipation of producing iron acyls of general structure **I**. In principle, these organometallic systems should be accessible via nucleophilic displacement of the acid chloride; however, acid halides of amino acids are not readily available using some of the common nitrogen protecting groups (e.g., Cbz, t-Boc).[4] In view of this limitation we sought an alternative method of carboxyl activation and describe herein are our preliminary findings.



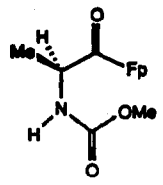
Fp = $Cp(CO)_2Fe$ eq. 1

In reviewing the tremendous number of methods available for carboxyl activation we felt that proceeding via the mixed carbonic anhydride was the method of choice.[5] We have found when using filtered, homogeneous solutions of the mixed carbonic anhydride, good to excellent yields of metal acyls can be obtained (equation 1, Table 1). This procedure is compatible with a variety of nitrogen protecting groups, including the base labile Fmoc ((9-fluorenyl-methyl) oxycarbonyl) group (entries 4 and 6) and can be extended to include dipeptides (e.g., Cbz-Pro-Phe → Cbz-Pro-Phe-Fp (84%)).

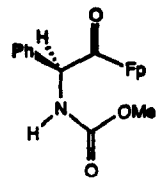
entry	Metal acyl	Yield	IR (CO, C=O cm^{-1})	^1H NMR (Cp-H)
1		60%	2018, 1969, 1930, 1698, 1633	4.99, 4.90
2		80%	2015, 1957, 1694, 1661	4.99, 4.87
3		86%	2020, 1965, 1719, 1653	4.90
4		56%	2030, 1966, 1722, 1655	4.89
5		86%	2020, 1960, 1716, 1643	4.90
6		91%	2020, 1960, 1718, 1643	4.91
7		86%	2025, 1960, 1715, 1650	4.91
8		78%	2010, 1965, 1718, 1640	4.88
9		67%	2029, 1965, 1721, 1643	4.92

In addition to the spectroscopic data reported all compounds were further characterized by [α]$^{D}_{25}$ along with ^{13}C NMR, Mass Spec (low resolution) and in some cases elemental analysis.

An obvious concern to us was the maintenance of the stereogenic center, and therefore NMR shift experiments were performed in an effort to evaluate the extent to which, if any, racemization had occurred during the course of the reaction. Preliminary studies using racemic Cbz-proline and Eu(hfc)$_3$ (Aldrich) resulted in partial resolution of the benzylic protons. However, the presence of rotomers complicated the 400MHz spectrum and we are unable to rigorously establish the enantiomeric purity of material prepared from optically active Cbz proline by this NMR technique. Seeking a chiral metal acyl that was more amenable to shift experiments we have prepared the alanine derivative II along with the phenyl glycine acyl III. The methyl urethane derivatives have been examined in detail and in each case, within the limits of detection there is no racemization.[6] Based on these examples, particularly in the case of III, we feel confident that the examples in Table 1 behave in an analogous fashion and are free of racemization.

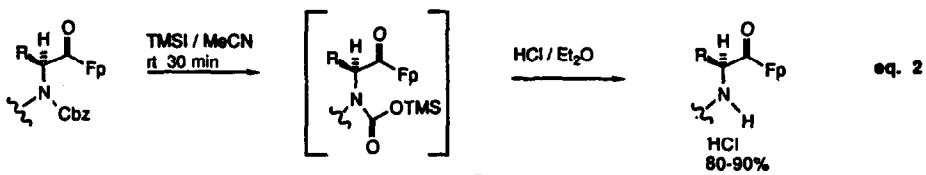


II (80%)

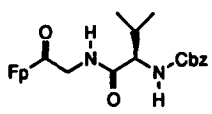


III (67%)

Initial studies to explore the utility of these novel acyls have focused on manipulating the nitrogen protecting group. Our rationale for choosing the Cbz derivatives rested on the premise that catalytic hydrogenation would lead to smooth deprotection while maintaining the metal-carbon bond. However, all attempts thus far have not produced the desired free amine, instead yielding only recovered starting material.[7] Fortunately iodotrimethylsilane (TMS-I, Aldrich) was found to smoothly effect deprotection with concomitant formation of the TMS-urethane (NMR).[8] This material is not isolated but efficiently converted to the hydrochloride salt upon treatment with HCl in dry ether (saturated solution, eq. 2). The hydrochloride salt is isolated as a pale yellow solid in excellent overall yield, easily manipulated in air and is best stored under nitrogen in the refrigerator (-5°C).

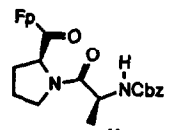


eq. 2



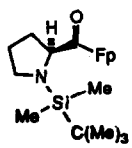
IV

62% from Cbz-Gly-Fp
83% from HCl salt



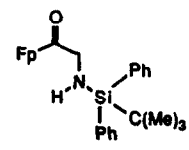
V

95% from HCl salt



VI

62% from HCl salt



VII

80% from HCl salt

Dissolving the hydrochloride salt in CH_2Cl_2 followed by in situ neutralization (triethylamine) liberates the free amine which undergoes smooth coupling to activated amino acids (mixed carbonic anhydride) to furnish the dipeptide derivatives **IV** and **V**. Likewise, treatment of the free amine with silylating agents can also be accomplished in excellent yields (see **VI** and **VII**). We are continuing to explore reactions of these metal acyls particularly **VI** and **VII** as metal carbene precursors.

A typical experimental procedure follows: In a two neck Schlenk flask was placed Cbz-proline (1.94g, 7.80 mmol) and THF (75 mL). The flask was cooled to 0°C and treated with

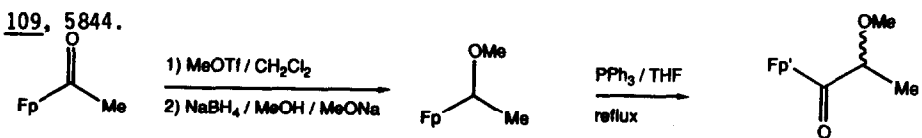
N-methylmorpholine (0.86 mL, 7.80 mmol) followed by isobutylchloroformate (1.01 mL, 7.80 mmol). The reaction was stirred for 15 minutes, cooled to -78°C and filtered (the filtrate was also maintained at -78°C). To this cold solution was added via syringe a 0.1M THF solution containing $Na[Fe(CO)_2Cp]$.[3] The reaction was allowed to proceed at this temperature (-78°C) for two hours and then warmed to room temperature and neutralized with degassed NH_4Cl (saturated solution). The volatile material was removed and the residue that remained was purified via flash chromatography (hexanes/ethyl acetate, 4/1). The yellow band was eluted and collected under a nitrogen atmosphere to minimize exposure to air (yellow orange oil, 2.7g, 87%).

Acknowledgement. We are grateful to Dr. Ron Nieman for his valuable assistance with the NMR experiments, and Dr. Jim Lehman for obtaining the mass spectral data. Special thanks to Susan Kaib and Mike Alvarado for preparing many of the protected amino acids used in this work. This work was supported by the Faculty Grant-In-Aid Program, Arizona State University and the Department of Chemistry at Arizona State University.

References and Notes

1) For an organocobalt acyl with a glycine derivative, see: Beck, W.; Petri, W. J. Organomet. Chem., 1977, 127, C40.

2) Formally this process requires reduction of the metal acyl followed by CO insertion. Using the simple model system 1, we have prepared 2 as a 1:1 mixture of diastereomers in approximately 35% overall yield (not optimized). For other examples of this type of process see: Forschner, T. C.; Cutler, A. R. Organometallics 1985, 4, 1247 and references therein. For an example of an organocobalt derived acyl participating in this kind of reaction sequence see: Tsu, C. C.; Cutler, A. R.; Kullnig, R. K. J. Am. Chem. Soc. 1987, 109, 5844.



1 2 Fp'=Cp(CO)PPh$_3$Fe

3) King, R. B. Inorg. Chem., 1963, 2, 531.

4) For the preparation of Fmoc acid chlorides see: Carpino, L. A.; Cohen, B. J.; Stevens, K. E.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langide, D. C. J. Org. Chem. 1986, 51, 3734.

5) In "The Peptides: Analysis, Synthesis and Biology," E. Gross and J. Meienhofer (eds.), Vol. 1, pp. 106-314, Academic Press, New York, 1979.

6) In the case of iron acyl II, the methyl singlet was clearly resolved in the presence of shift reagent, whereas, for iron acyl III the methine protons were separated by approximately 0.1 ppm in the presence of 10-50 mole % shift reagent.

7) To date hydrogenation conditions tried thus far include H_2/Pd/C (10%) in various solvents (THF, MeOH, EtOAc) and ammonium formate/Pd/C(10%) in MeOH. Control experiments have ruled out poisoning of the catalyst.

8) Jung, M. E.; Lyster, M. A., J. C. S. Chem. Commun. 1978, 315.

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