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A TRANSAMINATIVE SYNTHESIS OF 9-AMINO-9-FLUORENECARBOXYLIC ACID ESTERS

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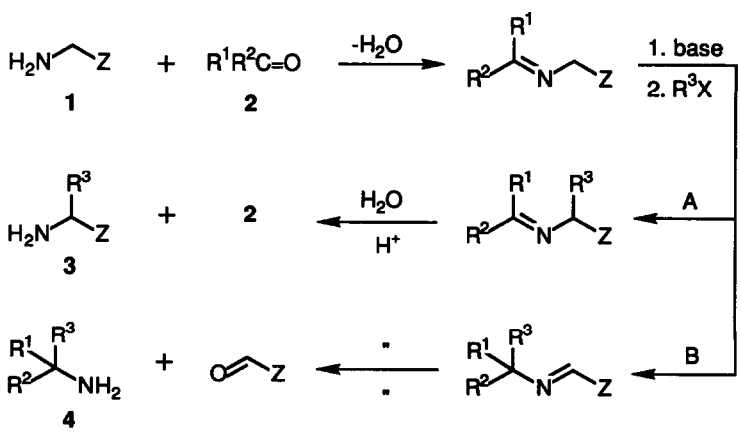
Summary. *The benzyl imines of several fluorenones were treated with base, followed by methyl chloroformate, to introduce the carbomethoxy group at the 9-fluorenyl position. Imine hydrolysis afforded the title compounds. The reaction was readily conducted on a 30-g scale.*

Glycine esters (**1**, Z = CO_2R) can be conveniently elaborated into higher α-amino acid esters **3** by conversion to their N-arylidene derivatives followed by alkylation (Scheme I, **2** = PhCHO or Ph_2CO).[1a,b] With few exceptions,[1c] the process occurs without allylic rearrangement (path A). The same regiochemistry prevails if Z = CN[2a] or C≡CSiMe_3.[2b] By contrast, in biomimetic transamination reactions,[3] an appropriate choice of substituents promotes tautomerization (path B, R^3 = H), to interconvert amines and carbonyl compounds as in the biosynthesis of α-amino acids (**2->4**, $R^2 = CO_2H$, R^3 = H). Herein we report a new variant in which **2** is a fluorenone, Z is phenyl, and R^3X is methyl chloroformate. The reaction follows path B to afford a practical, high-yielding synthesis of 9-amino-9-fluorenecarboxylic acid esters (**4**, $R^3 = CO_2CH_3$).

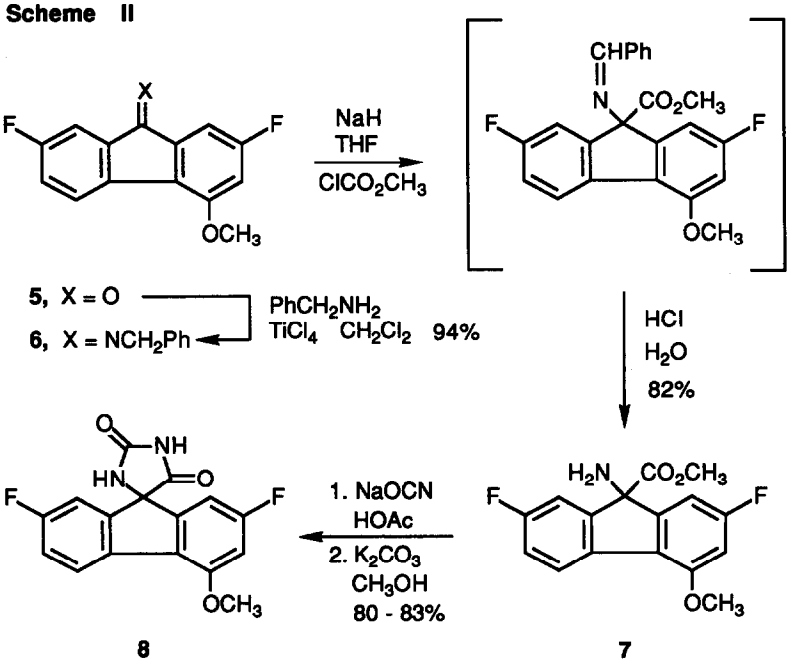
Scheme I



In the course of research on fluorenone-derived spirohydantoins as aldose reductase inhibitors for treatment of chronic complications of diabetes,[4] we required 25 g of each enantiomer of **8** (Scheme II). Attempts to resolve racemic **8**, prepared by Bucherer-Bergs reaction on fluorenone **5**,[5a] were unsuccessful. Racemic amino ester **7**, however, could be resolved efficiently by preparative HPLC on a Chiralcel OF cellulose carbamate - silica gel column,[5b] using 2 : 1 hexane: *i*-PrOH eluant.[5c] The resolved enantiomers of **7** were converted as shown[6a] to (+)-**8** and (-)-**8**.

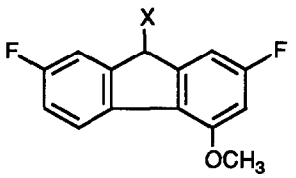
We therefore devised the streamlined[6b] transamination-carbomethoxylation sequence **5->6->7.** Ketone **5** was treated with benzylamine and $TiCl_4$,[9a] both in 25% excess, to give imine **6** (94%). A solution of **6** in anhydrous THF[10] was treated with sodium hydride, generating a deep red anion. Addition of methyl chloroformate, followed by acidic hydrolysis, afforded **7** in 82% yield after purification. This method proved convenient for preparing **7** in 20 - 25 g lots. Starting ketone **5** (~5%) and amine **10** (~2%) were consistently obtained as side products, despite the use of excess base. These may arise from carbomethoxylation at the benzylic position (i.e., path A), followed by deprotonation to form a stable imino ester anion which is hydrolyzed on workup. However, no α-phenylglycine methyl ester (**3**, path A) was detected in the crude product.

Scheme II

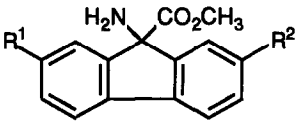


8 **7**

To test the scope of the process, amino esters **11 - 13** were prepared from the corresponding fluorenones. Yields shown are for the carbomethoxylation/hydrolysis step. The fluoro compounds **11** and **12** were readily secured by the procedure described above. In the unsubstituted case, LDA was required to form the anion efficiently, and the product **13**[8c] was obtained in diminished yield.[11]



9, X = CO_2CH_3
10, X = NH_2



11, $R^1 = R^2 = F$ 82%
12, $R^1 = F$, $R^2 = H$ 87%
13, $R^1 = R^2 = H$ 64%

That the reaction occurs principally at the 9-fluorenyl position is consistent with the expected charge distribution in the delocalized anion. Fortunately, the fluoro substituents brought the acidity of **6** into a convenient range.[12] Finally, these results suggest that substituted fluorenones may find further use as reagents for converting amines to carbonyl compounds.

Imine 6.[9a] $TiCl_4$ (1.0 M in CH_2Cl_2, 127 mL) was added dropwise over 15 min to a stirred suspension of ketone **5** (50.0 g, 0.203 mol) and benzylamine (81 g, 0.76 mol) in 1.0 L of CH_2Cl_2 under N_2, keeping the temperature below 15 °C.[9b] The mixture was stirred for 30 min while warming to 24 °C, then filtered through Florisil, washing with 4 L of ether. The filtrate was concentrated to 500 mL and diluted with 500 mL of hexane. The precipitated yellow imine **6** was collected by filtration. The filtrate was further concentrated to provide a second and third crop. The combined yield of **6** after drying was 64.0 g (94%, 5 : 4 mixture of double bond isomers).

Amino ester 7. Imine **6** (30.0 g, 0.0896 mol) was added in portions, over 5 min, to a stirred suspension of NaH (4.5 g of a 60% oil dispersion, 0.11 mol, 2 x hexane washed) in 300 mL of anhydrous THF[10] at 45 °C under N_2. Hydrogen evolution ceased after 20 min; the mixture was stirred for an additional 20 min, then cooled to 10 °C. A solution of $ClCO_2CH_3$ (21 mL, 0.27 mol) in 40 mL of anhydrous THF[10] was stirred over anhydrous K_2CO_3 under N_2 for 1 min, decanted, and added, keeping the temperature below 12 °C. The mixture was stirred for 1 h while warming to 24 °C, then cooled to 10 °C, quenched with 100 mL of 1 N HCl, and stirred (to 24 °C) for 1 h. The mixture was diluted with 500 mL of 1 : 1 ether-hexane and the amine hydrochloride was extracted with 1 N HCl. The aqueous solution was basified ($NaHCO_3$) and the precipitated product was collected by filtration. The solid was dissolved in 800 mL of EtOAc and the solution was dried ($MgSO_4$), treated with Norit A , filtered through Celite and concentrated. The residue was triturated with ether, then recrystallized (EtOAc-hexane), affording 20.7 g (76%) of **7**, m.p. 153-155 °C. The supernatant was concentrated and the residue chromatographed on silica (CH_2Cl_2 --> 5% CH_3OH in CH_2Cl_2) to give an additional 1.6 g (6%) of **7**, m.p. 150-152 °C.

References and Notes

1. (a) O'Donnell, M. J.; Bennett, W. D.; Shengde Wu *J. Am. Chem. Soc.* **1989**, *111*, 2353, and cited references.
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   (c) Harris, C. J. *Tetrahedron Lett.* **1981**, *22*, 4863. Bey, P.; Ducep, J. B.; Schirlin, D. *Tetrahedron Lett.* **1984**, *25*, 5657. Compare: Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Kolhe, J. N.; Perry, M. W. D.; Jain, A. U. *Tetrahedron* **1986**, *42*, 4223, and following papers.
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5. (a) American Tokyo Kasei, Inc.
   (b) Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Chromatogr.* **1986**, *363*, 173. *Idem., J. Am. Chem. Soc.* **1984**, *106*, 5357.
   (c) Separation performed by Daicel Chemical Industries, Ltd., New York.
6. (a) Experimental details, physical properties of (+)-**7**, (-)-**7**, (+)-**8** and (-)-**8**, and biological properties of (+)-**8** and (-)-**8**, will be provided in a separate paper.
   (b) Racemic **7** was first prepared from ketone **5** by a lengthy route: (1) H_2NNH_2, $(HOCH_2CH_2)_2O$, 180 °C [7] (2) BuLi, THF; CO_2 (3) CH_3OH, H^+ (giving ester **9**) (4) NaH, THF, 0 °C; NCS, -70 °C (5) NaN_3, DMF (6) cyclohexene, EtOH, 10% Pd-C, reflux. Alternatively, gram-scale reactions of sodio-**9** with the O-mesitylenesulfonyl[8a,b] or -2,4-dinitrophenyl[8c] derivatives of hydroxylamine gave **7** in good yields, and shortened the process to four steps, but scaleup proved impractical.
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8. (a) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133.
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9. (a) Fieser and Fieser, "Reagents for Organic Synthesis" *2*, 414; *3*, 291.
   (b) If the temperature exceeded 15 °C during the addition of benzylamine, a side product with spectra suggesting the dibenzyl aminal of **5** was also produced.
10. Best results were obtained using THF dried over $LiAlH_4$ under N_2 and distilled into the reaction flask.
11. Amino esters **7**, **11** (m.p. 128-129 °C), **12** (m.p. 82-84 °C) and **13** (m.p. 107-108 °C, lit.[8c] m.p. 113 °C) were fully characterized by ^1H NMR, IR, MS and combustion analysis. The precursor imines gave satisfactory ^1H NMR (and for **6**, IR) spectra.
12. Bordwell, F. G.; McCollum, G. J. *J. Org. Chem.* **1976**, *41*, 2391; also see footnote 7g in reference 1a above.

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