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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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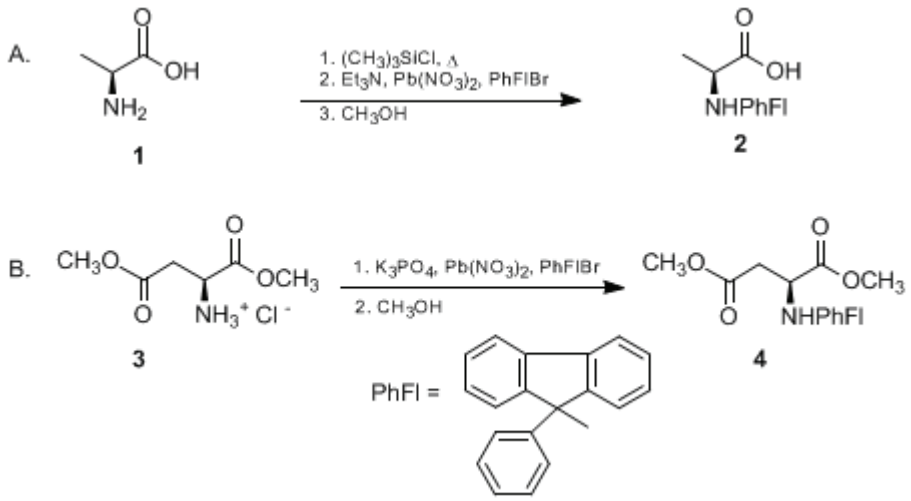
(S)-N-(9-PHENYLFLUOREN-9-YL)ALANINE AND (S)-DIMETHYL N-(9-PHENYLFLUOREN-9-YL)ASPARTATE

[L-Alanine, N-(9-phenyl-9H-fluoren-9-yl)- and L-Aspartic acid, N-(9-phenyl-9H-fluoren-9-yl-, dimethyl ester]



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1. Procedure

*Caution! Chlorotrimethylsilane is moisture-sensitive and should be kept under an inert atmosphere at all times. Persons following this procedure should be thoroughly familiar with the handling of moisture-sensitive materials. Lead nitrate [$Pb(NO_3)_2$] is toxic (**1**), and it and tripotassium phosphate (K_3PO_4) are hygroscopic.*

A. *(S)-N-(9-Phenylfluoren-9-yl)alanine* (**2**).[3] A 1-L, flame-dried, three-necked Morton flask (Note 1) equipped with an overhead stirrer, rubber septum, and reflux condenser (equipped with a rubber septum) under a nitrogen atmosphere is charged with L-alanine (**1**, 13.5 g, 150 mmol, (Note 2)), chloroform (375 mL, (Note 3)), acetonitrile (75 mL, (Note 4)), and chlorotrimethylsilane (19.04 mL, 150 mmol, (Note 5)). The rubber septum in the neck of the Morton flask is replaced with a glass stopper, and the mixture is heated at reflux for 2 hr with vigorous stirring under an inert atmosphere (Note 6). The mixture is cooled to room temperature under a stream of nitrogen, triethylamine (46.0 mL, 330 mmol, (Note 7)) is added via syringe at a rate sufficient to maintain a gentle reflux, and the mixture is stirred for 15 min after which $Pb(NO_3)_2$ (33.1 g, 100 mmol, (Note 8)) is added. The glass stopper is replaced with a rubber septum, and a solution of 9-bromo-9-phenylfluorene (57.8 g, 180 mmol, (Note 9)) in chloroform (180 mL, (Note 3)) is added via a Teflon cannula with a positive nitrogen pressure. The reflux condenser is replaced with a glass stopper, and an 18-gauge syringe needle equipped with an argon-filled balloon is inserted in the rubber septum. The heterogeneous, off-white mixture is stirred vigorously under this inert atmosphere for 48 hr. After about 20 hr, the reaction mixture becomes orange and darkens over time. Methanol (15.2 mL, 375 mmol, (Note 10)) is then added, and the mixture is stirred an additional 30 min.

The mixture is filtered using a sintered glass filter, the filter cake is washed by stirring with chloroform (3 × 50 mL), and the dark orange filtrate is evaporated to a residue that is partitioned between ether (750 mL, (Note 11)) and aqueous 5% citric acid (750 mL, (Note 12)). The layers are

separated, and the aqueous layer is extracted with ether (4 × 250 mL). The combined organic solutions are extracted with 1 M sodium hydroxide (300 mL). The aqueous solution is washed with 300 mL of ether, cooled to 0°C with stirring using a magnetic stir bar, and the pH is adjusted to 7 by the dropwise addition of glacial acetic acid (approximately 17 mL, (Note 13)). The mixture now containing an off-white precipitate is extracted with 25% 2-propanol (Note 14) in chloroform (3 × 300 mL). The combined organic solutions are washed with 150 mL of saturated sodium chloride solution, dried (Na_2SO_4), filtered, and evaporated to a light yellow foam that is dried under reduced pressure to give 39.2 g (80% yield) of (S)-N-(9-phenylfluoren-9-yl)alanine (**2**) (Note 15).

B. *(S)-Dimethyl N-(9-phenylfluoren-9-yl)aspartate* (**4**).[4] A 1-L, flame-dried, three-necked Morton flask (Note 1) equipped with an overhead stirrer and two rubber septa under a nitrogen atmosphere is charged with $Pb(NO_3)_2$ (28.2 g, 85.0 mmol, (Note 8)), K_3PO_4 (44.6 g, 210 mmol, (Note 16)), and acetonitrile (250 mL, (Note 4)). (S)-Dimethyl aspartate hydrochloride (**3**, 19.8 g, 100 mmol, (Note 17)) is added, followed by 9-bromo-9-phenylfluorene (40.15 g, 125 mmol, (Note 9)). The off-white, heterogeneous mixture is stirred vigorously for 22 hr, and to the mixture is added methanol (40.5 mL, 1.00 mol, (Note 10)); the mixture is stirred an additional 30 min and filtered through approximately 20 g of diatomaceous earth ("Celite") on a sintered glass funnel. The filter cake is washed by stirring with portions of chloroform until no UV chromophore can be detected in the filtrate (Note 18). Silica (60 g, (Note 19)) is added to the combined organic solutions, and the solvent is removed (rotary evaporator), leaving a dry powder. This powder is added to a column of silica (800 g, (Note 19)) and the column is eluted with 10% ethyl acetate in hexanes (Note 20) to give 9-methoxy-9-phenylfluorene (5.30 g, 19.5 mmol, (Note 21)) and then 9-phenyl-9-fluorenol (2.00 g, 7.7 mmol, (Note 22)). A 1/1 mixture of 9-phenyl-9-fluorenol and **4** is eluted next (2.13 g). After all the 9-phenyl-9-fluorenol has been eluted, the eluting solvent is changed to 25% ethyl acetate in hexanes (Note 20). The combined solutions of pure **4** are evaporated (rotary evaporator), yielding (S)-dimethyl N-(9-phenylfluoren-9-yl)aspartate (**4**) as a light yellow solid (36.1 g, 90 mmol, 90% yield, (Note 23)) after drying for 1 day at 0.1 mm. The 2.13-g mixture of **4** and 9-phenyl-9-fluorenol can be rechromatographed (100 g of silica, 10–25% ethyl acetate in hexane) to give an additional 0.8 g (3.1 mmol) of 9-phenyl-9-fluorenol (for a total of 2.80 g, 10.8 mmol) and 1.3 g (3.2 mmol, 3.2% yield) of **4**, for a total of 37.4 g (93% yield) of **4**.

2. Notes

1. Use of a Morton flask and an overhead stirrer allows for better mixing of the heterogenous system and gives conversion to product faster than does use of a standard round-bottomed flask with an overhead stirrer.
2. L-Alanine was purchased from Fisher Scientific company and used without further purification.
3. Chloroform was purchased from Fisher Scientific Company and distilled from phosphorus oxide (P_2O_5) immediately before use and added to the reaction mixture via syringe.
4. Acetonitrile was purchased from EM Science, distilled from calcium hydride (CaH_2) immediately before use and added to the reaction mixture via syringe.
5. Chlorotrimethylsilane was purchased from Aldrich Chemical Company, Inc., distilled from CaH_2 immediately before use, and added to the reaction mixture via syringe.
6. A syringe needle equipped with an argon-filled balloon should be inserted through the rubber septum on the reflux condenser. In addition, while the mixture is refluxing, the apparatus should be checked frequently for leaks.
7. Triethylamine was purchased from Fisher Scientific Company and distilled from barium oxide (BaO) immediately before use and added to the reaction mixture via syringe.
8. Lead nitrate (toxic!) was purchased from Fisher Scientific Company, dried in an oven at 160°C for 4 days, and cooled in a desiccator, yielding a freely-flowing, white granular solid. The checkers dried it at 100°C under 1.5 mm vacuum for 4 days.
9. 9-Bromo-9-phenylfluorene was prepared as described.[5]
10. Methanol was purchased from Fisher Scientific Company and used without further purification.
11. Ethyl ether was purchased from Fisher Scientific Company and used without further purification.
12. An insoluble brownish-orange polymer formed was carefully excluded from the organic extractions. Leaching of this material into the organic layer produces colored product.
13. Glacial acetic acid was purchased from Fisher Scientific Company and used without further purification. Near pH 7, much of the product precipitated, and the off-white mixture became difficult to

stir. Distribution of the acetic acid was accomplished by manually swirling the flask.
14. 2-Propanol was purchased from Fisher Scientific Company and used without further purification.
15. Compound **2**[3] thus obtained was of sufficient purity (>97%, as determined by elemental analysis) for direct use; but was contaminated by a small amount of highly colored impurities. IR cm^{-1}: 3070 (m), 3005 (m), 2905 (m), 1765 (m), 1735 (m), 1640 (m), 1590 (m), 1450 (s), 1390 (s), 1375 (s), 1355 (s), 690 (m), 605 (m). **2** can be recrystallized (1:1 EtOAc/hexane) to give a white solid,[3] mp 158–161°C. [α] −63.0° (EtOH, *c* 1.4); ^{1}H NMR δ: 1.09 (d, 3 H, J = 7.2), 2.70 (q, 1 H, J = 7.2), 7.36 (m, 11 H), 7.71 (m, 2 H); ^{13}C NMR δ: 19.2, 52.9, 73.0, 120.19, 120.21, 125.5, 125.7, 125.9, 127.6, 128.2, 128.6, 129.1, 140.5, 140.6, 141.8, 145.9, 146.5, 176.5 (Four ^{13}C NMR signals appear to be missing, possibly due to overlapping of signals.); TLC R_f 0.25 (~8:1 EtOAc/hexane); UV (EtOH) λ, nm (ε): 310 (9,600), 298 (5,000), 266 (14,000), 238 (23,000), 209 (47,000). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.4; H, 5.6; N, 4.2.
16. Potassium phosphate was obtained from Mallinckrodt Chemical and was dried at >500°C for > 12 hr, cooled in a desiccator, ground to a *fine powder* with a mortar and pestle, and stored in a desiccator before use. It must be weighed quickly, as it is hygroscopic.
17. (S)-Dimethyl aspartate hydrochloride was prepared as described[4] and recrystallized from acetone to give a white crystalline solid (mp 114.5–115°C, lit.[6] mp 116–117°C), which was stored in a vacuum desiccator before use.
18. Eight or nine 100-mL portions of chloroform, obtained from EM Science and used without further purification, were required.
19. Silica gel of 230–400 mesh was obtained from EM Science. The checkers used silica gel from J. T. Baker.
20. Both ethyl acetate and hexanes were obtained from Fisher Scientific Company and used without further purification.
21. The physical properties of 9-methoxy-9-phenylfluorene are as follows:[7] mp 93–94°C (lit.[7] mp 94–95°C), ^{1}H NMR δ: 2.96 (s, 3 H), 7.2–7.4 (m, 11 H), 7.7 (m, 2 H); ^{13}C NMR δ: 51.3, 89.0, 119.9, 125.3, 125.5, 127.1, 128.0, 128.1, 128.9, 140,8, 143.4, 146.8; TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.85.
22. The properties of 9-phenyl-9-fluorenol are as follows: TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.67; see ref. [5] for additional spectral and physical data.
23. The physical properties of (S)-dimethyl N-(9-phenylfluoren-9-yl)aspartate (**4**) are as follows:[4] mp 58–59.5°C (sometimes **4** does not solidify); $[\alpha]_D$ −264° ($CHCl_3$, *c* 3.3); IR ($CHCl_3$) cm^{-1}: 3320 (w), 3005 (m), 2950 (m), 1740 (s), 1600 (w), 1440 (s), 1365 (m), 1340 (m), 1170 (m), 1010 (m), 1000 (m), 900 (w), 690 (m), 610 (w); UV (EtOH) λ (ε): 310 (9,600), 298 (8,700), 276 (22,100), 239 (43,700), 231 (50,700), 211 (66, 200); ^{1}H NMR δ: 2.35 (dd, 1 H, J = 15, 5.4), 2.52 (dd, 1 H, J = 15, 6.8), 3.01 (m, 1 H), 3.3 (br s, 1 H), 3.34 (s, 3 H), 3.65 (s, 3 H), 7.15–7.4 (m, 11 H), 7.7–7.8 (m, 2 H); ^{13}C NMR δ: 39.7, 51.5, 51.8, 52.7, 72.7, 119.7, 119.9, 125.4, 125.8, 125.9, 127.2, 127.4, 127.7, 128.2, 128.3, 139.7, 141.1, 144.4, 148.3, 148.5, 170.8, 174.6 (Note: Three ^{13}C NMR signals appear to be missing, possibly due to overlapping of signals.); TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.52. Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.6; H, 5.8; N, 3.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Procedures A and B illustrate the two current methods for preparation of N-9-phenylfluoren-9-yl derivatives of amino acids and amino acid esters. Free carboxylate (as in alanine in Step A) or free hydroxyl (e.g., serine[8]) functions can be blocked for the duration of the reaction as trimethylsilyl (TMS) esters or ethers, respectively, by treatment with chlorotrimethylsilane and triethylamine. The TMS group(s) are then removed by methanolysis from carboxylic acids (as in Step A) and mild acidic hydrolysis from hydroxyl groups, both being accomplished during product isolation. In addition to **2**, the N-9-phenylfluoren-9-yl derivatives of serine,[8] glutamic acid γ-methyl ester,[9] and aspartic acid β-methyl ester[4,10] have been prepared in this manner.

Substrates whose only reactive nucleophile is an amino group can be alkylated with 9-bromo-9-phenylfluorene using the method described in Step B. In addition to **4**, the N-9-phenylfluoren-9-yl derivatives of glutamate diesters,[9] aziridines,[11] and N-alkyl aspartate diesters[4,12,13] have been prepared by this method.

Exclusion of moisture from the reagents and apparatus is most important, as 9-bromo-9-phenylfluorene hydrolyzes to 9-phenyl-9-fluorenol, which is unreactive toward free amines. Accordingly, all glassware, K_3PO_4, $Pb(NO_3)_2$ (which scavenges bromide ion), and substrates must be dried thoroughly (as described above) and kept under an inert atmosphere prior to use. In addition, solvents must be distilled immediately before use and transferred to the reaction vessel under an inert atmosphere.

The methanol quench in Step B facilitates chromatographic purification by forming the known 9-methoxy-9-phenylfluorene,[7] which is less polar than 9-phenyl-9-fluorenol, from 9-bromo-9-phenylfluorene (but not from 9-phenyl-9-fluorenol). Both 9-methoxy-9-phenylfluorene and 9-phenyl-9-fluorenol can be converted to 9-bromo-9-phenylfluorene by treatment with 48% hydrobromic acid (HBr).[5]

Both the stability[14] and rigid steric bulk of the 9-phenylfluoren-9-yl group have increased significantly the utility of amino acids N-protected in this way as chiral educts for asymmetric synthesis. N-(9-Phenylfluoren-9-yl)-α-amino aldehydes maintain configurational stability at the αcarbon during treatment with silica gel or triethylamine and on treatment with Wittig and organometallic reagents.[3,8,15,16] N-(9-Phenylfluoren-9-yl)-α-amino ketones and esters behave similarly under these conditions, and they can also be regioselectively enolized and subsequently alkylated with a variety of electrophiles in good to excellent yield with modest to excellent diastereoselectivity, no detectable racemization, and no detectable alkylation on nitrogen or at the carbon corresponding to the αcarbon of the starting amino acid.[4,9,10,11,12,13,15,16] Consequently, these N-(9-phenylfluoren-9-yl)-α-amino carbonyl compounds have enabled the enantiospecific syntheses of many important compounds, including cyclosporin's unique amino acid MeBmt,[16] other unusual amino acids,[9,10] α-amino aldehydes,[3,8,15,16] vinca alkaloids,[4,12] (−)-vindoline,[13,17] α-alkyl branched carboxylic acids,[15] and the core nuclei of two antineoplastic agents.[11]

Removal of the 9-phenylfluoren-9-yl group has been accomplished by three different procedures: acidolysis with trifluoroacetic acid,[3,9,11,12,13] catalytic hydrogenolysis,[4,8,10,15,16] and dissolving metal reduction.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 103

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

silica

L-Aspartic acid, N-(9-phenyl-9H-fluoren-9-yl-, dimethyl ester

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

citric acid (77-92-9)

chloroform (67-66-3)

sodium chloride (7647-14-5)

alanine,
L-alanine (56-41-7)

HYDROBROMIC ACID (10035-10-6)

barium oxide

nitrogen (7727-37-9)

aluminum (7429-90-5)

acetone (67-64-1)

carbon (7782-42-5)

2-propanol (67-63-0)

lead nitrate (10099-74-8)

hexane (110-54-3)

serine (56-45-1)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

trifluoroacetic acid (76-05-1)

CHLOROTRIMETHYLSILANE (75-77-4)

phosphorus oxide (1314-56-3)

9-Bromo-9-phenylfluorene (55135-66-5)

9-Phenyl-9-fluorenol (25603-67-2)

potassium phosphate,
tripotassium phosphate (7778-53-2)

(S)-N-(9-Phenylfluoren-9-yl)alanine,
L-Alanine, N-(9-phenyl-9H-fluoren-9-yl)- (105519-71-9)

(S)-Dimethyl N-(9-phenylfluoren-9-yl)aspartate (120230-62-8)

9-methoxy-9-phenylfluorene

(S)-Dimethyl aspartate hydrochloride