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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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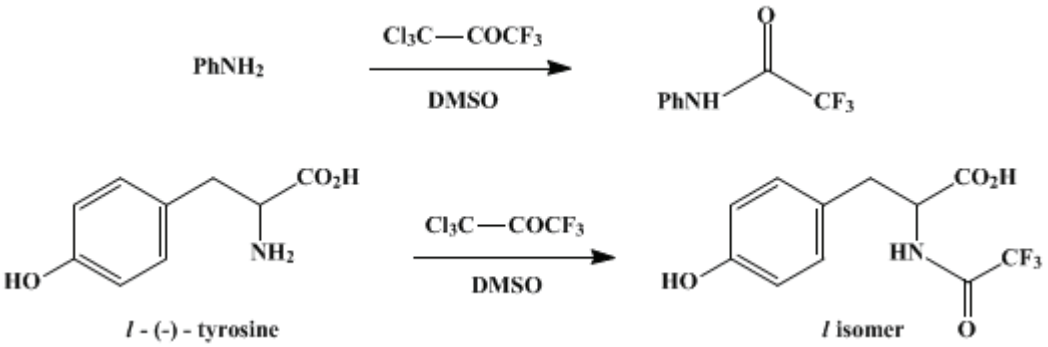
TRIFLUOROACETYLATION OF AMINES AND AMINO ACIDS UNDER NEUTRAL, MILD CONDITIONS: *N*-TRIFLUOROACETANILIDE AND *N*-TRIFLUOROACETYL-L-TYROSINE

[Acetamide, 2,2,2-trifluoro-*N*-phenyl- and L-Tyrosine, *N*-(trifluoroacetyl)-]



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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. N-*Trifluoroacetanilide*. A two-necked, round-bottomed flask fitted with a thermometer, a Drierite tube, and a magnetic stirring bar is charged with 4.66 g. (4.56 ml., 0.0501 mole) of aniline (Note 1) and 15 ml. of dimethyl sulfoxide (Note 2). The resulting solution is stirred and cooled in an ice water bath, and when the internal temperature has dropped to 10–15°, 21.5 g. (0.0998 mole) of 1,1,1-trichloro-3,3,3-trifluoroacetone (Note 3) is added in portions through the condenser. A mild exotherm results, and the addition is extended over *ca.* 5 minutes, maintaining a reaction temperature below 40°. When the addition is complete, the ice bath is removed, and the amber solution is stirred at room temperature for 22 hours. The reaction mixture is poured into 750 ml. of water. A crystalline solid separates, and the resulting slurry is stirred for 1 hour before filtration. After being washed with water, the crystals are dried in a vacuum oven at 50° for 40 minutes, giving 6.49–6.53 g. (69%) of *N*-trifluoroacetanilide, m.p. 86.0–86.5° (cor.) (Note 4),(Note 5),(Note 6).

B. N-*Trifluoroacetyl*-L-*tyrosine*. A two-necked, round-bottomed flask fitted with a thermometer, a condenser protected with a Drierite tube, and a magnetic stirrer is charged with 18.12 g. (0.1001 mole) of L-(−)-tyrosine (Note 7) and 130 ml. of dimethyl sulfoxide (Note 2). The suspension is stirred and cooled in an ice water bath. When the internal temperature reaches 10–15°, 64.62 g. (0.2999 mole) of 1,1,1-trichloro-3,3,3-trifluoroacetone (Note 3) is added through the condenser at a rate such that the temperature of the reaction temperature does not exceed 35°. The cooling bath is removed, and the reaction mixture is stirred at room temperature for 22 hours, during which time the suspension becomes a solution. This solution is poured into 660 ml. of ice water, and the resulting mixture is extracted with two portions (660 ml. and 400 ml.) of 1-butanol. The organic extracts are concentrated, first on the rotary evaporator and then at 40° (0.1 mm.), giving a red-orange semisolid, which is dissolved in a minimum amount of acetone and placed on a column of silica gel (Note 8). Elution with benzene–acetone mixtures (Note 9) provides 20.0–22.2 g. (72–80%) of *N*-trifluoroacetyl-L-tyrosine as a colorless to light yellow solid. Recrystallization from either benzene–acetone or water gives white needles, m.p.

192.5–193.5° (cor.) (Note 6) and (Note 10).

2. Notes

1. Commercial aniline from Fisher Scientific Company (purified grade) was used as supplied.
2. Dimethyl sulfoxide from the J. T. Baker Chemical Company (reagent grade) was used as supplied.
3. 1,1,1-Trichloro-3,3,3-trifluoroacetone is available from PCR, Inc., P.O. Box 14318, Gainesville, Florida. It may also be prepared easily by the following procedure. Fresh, anhydrous aluminum chloride (18.5 g., 0.139 mole) and 35.0 g. (0.192 mole) of chloropentafluoroacetone (b.p. 7.8°; available from PCR, Inc., or Allied Chemical Corp.) are combined in a flask fitted with a dry ice condenser and a magnetic stirring bar. The refluxing mixture is stirred for 4–6 hours and allowed to warm gradually to room temperature. The contents of the flask are extracted three times with anhydrous ether, and the combined extracts are distilled at atmospheric pressure. After the ether has been removed, continued distillation gives 22.8–28.5 g. (55–69%) of 1,1,1-trichloro-3,3,3-trifluoroacetone, b.p. 83.5–84.5°; IR (film) 1790 $cm.^{-1}$. This compound is stored at room temperature in a tightly stoppered bottle. In the absence of reliable toxicity data, it should be handled with normal precautions.
4. IR (CH_2Cl_2) $cm.^{-1}$: 3401 and 3049 (NH, CH), 1740 (C=O), 1235 (C-F), (lit.,[2] m.p. 87.6°).
5. The checkers suspected that some product was lost during the drying process. Therefore, they purified the crude product by sublimation at 55° (0.15 mm.), which gave 3.76–3.84 g. (80–81%) of *N*-trifluoroacetanilide in half-scale runs (Note 6).
6. The checkers ran Parts A and B at half the submitter's scale, and the yields were comparable or higher in all cases.
7. Reagent-grade L-(−)-tyrosine was obtained from Fisher Scientific Company.
8. Silica gel 60 (70–230 mesh) was purchased from E. Merck, Darmstadt, Germany.
9. The checkers, working at one half the submitter's scale, obtained 17.5 g. of crude product and used 175 g. of silica gel in their column. They eluted as follows:

Fraction	Eluent (Benzene: Acetone Ratio, ml.)	Eluate
1	9:1, 425	1.2 g., yellow oil
2	17:3, 100	1.7 g., pale yellow solid, m.p. 85–92°
3	3:1, 850	9.4 g., colorless solid, m.p. 194–196°
4	3:2, 600	0.4 g., colorless solid, m.p. 209–212°

Fraction 2 was recrystallized from benzene–acetone to give 1.2 g. of colorless solid, m.p. 194–196° (uncor.), which was combined with fraction 3 to give 10.6 g. (76%) of product.
10. IR (Nujol) $cm.^{-1}$: 1695 (C=O), 1180 (C-F), (lit.,[3] m.p. 192.5–193.5°).

3. Discussion

The original procedure for the trifluoroacetylation of amino acids used trifluoroacetic anhydride,[4] which, although inexpensive and readily available, has certain disadvantages: it is a highly reactive compound and has caused undesired reactions such as the cleavage of amide or peptide bonds;[5] unsymmetrical anhydrides are formed between the newly formed *N*-trifluoroacetylamino acids and the by-product trifluoroacetic acid; and excess trifluoroacetic anhydride has caused racemization of asymmetric centers.

Thus, other trifluoroacetylation reagents have been investigated. *S*-Ethyl trifluorothioacetate[6] has none of the above disadvantages. It does require, however, weakly basic conditions (pH 8–9) and an aqueous medium. Phenyl trifluoroacetate[7] effects trifluoroacetylation of amino acids under essentially neutral conditions. Its main disadvantages are high cost and the elevated temperatures (120–150°) required.

1,1,1-Trichloro-3,3,3-trifluoroacetone is a relatively unreactive compound that is volatile and easily handled. It may be obtained either commercially or by a simple laboratory preparation (Note 3), and it trifluoroacetylates amino groups in amino acids and other compounds under neutral and extremely mild

conditions.[8] Table I lists some compounds that have been prepared with this reagent.

TABLE I
TRIFLUOROACETYLAMINO COMPOUNDS PREPARED WITH CF_3COCCl_3[a]

Product	Yield (%)
TFA-Aniline	69
TFA-L-Valine	94
TFA-DL-Phenylalanine	52
TFA-L-Phenylalanine	57
TFA-L-Leucine	100
TFA-L-Tyrosine	80
TFA-L-Proline	100
TFA-DL-Alanine	20
TFA-Glycylglycine	43
TFA-L-Prolyglycine, ethyl ester	23
TFA-L-Asparagine	26
TFA-Dehydroabietylamine	11

[a] Except for the first entry, all the compounds listed were prepared by the procedure of Part B.

References and Notes

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

L-(−)-tyrosine

N-trifluoroacetylamino acids

TFA-L-Prolyglycine, ethyl

TFA-Dehydroabietylamine

Benzene (71-43-2)

ether (60-29-7)

aniline (62-53-3)

1-butanol (71-36-3)

acetone (67-64-1)

aluminum chloride (3495-54-3)

dimethyl sulfoxide (67-68-5)

trifluoroacetic acid (76-05-1)

trifluoroacetic anhydride (407-25-0)

1,1,1-trichloro-3,3,3-trifluoroacetone (758-42-9)

chloropentafluoroacetone (79-53-8)

TFA-Aniline,
Acetamide, 2,2,2-trifluoro-N-phenyl- (404-24-0)

TFA-Glycylglycine (400-58-8)

Phenyl trifluoroacetate (500-73-2)

N-Trifluoroacetanilide

N-Trifluoroacetyl-L-tyrosine,
L-Tyrosine, N-(trifluoroacetyl)-,
TFA-L-Tyrosine (350-10-7)

S-Ethyl trifluorothioacetate (383-64-2)

TFA-L-Valine

TFA-DL-Phenylalanine

TFA-L-Phenylalanine

TFA-L-Leucine

TFA-L-Proline

TFA-DL-Alanine

TFA-L-Asparagine