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Note

A simplified synthesis of 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate

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Summary

2,3,5,6-Tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate has been synthesized via an improved route which involves the direct coupling of 2-(2-nitroimidazol-1-yl) acetic acid with 2,3,5,6-tetrafluorophenol. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: Hypoxia; Nitroimidazole; Fluoroetanidazole; EF3

Introduction and Discussion

Fluorine-18 labelled 2-nitroimidazoles are used in the visualization of hypoxic tissue by positron emission tomography.[1] 2,3,5,6-Tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate is a precursor used in the synthesis of hypoxia markers such as *N*-(2-[^{18}F]fluoroethyl)-2-(2-nitroimidazol-1-yl)-acetamide ([^{18}F] fluoroetanidazole)[2] and 2-(2-nitroimidazol-1-yl)-*N*-([^{18}F]3,3,3-trifluoropropyl)-acetamide ([^{18}F] EF3).[3]

The current literature method for producing this precursor involves the synthesis of 2,3,5,6-tetrafluorophenyl trifluoroacetate over 5 days,[4] followed by reaction with 2-(2-nitroimidazol-1-yl) acetic acid.[2,3] This procedure appeared to be unnecessarily lengthy, given that 2,3,5,6-

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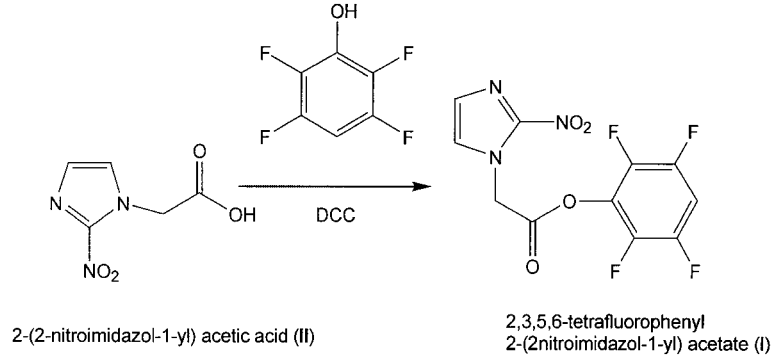
tetrafluorophenol may be directly coupled to other carboxylic acids using 1,3-dicyclohexylcarbodiimide (DCC).[5] This note reports a simple synthesis of 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate (**I**) from 2-(2-nitroimidazol-1-yl) acetic acid (**II**) and commercially available 2,3,5,6-tetrafluorophenol (Scheme 1)



Scheme 1.

Experimental

Reagents, including anhydrous solvents, were obtained from Aldrich. ^{1}H (500 MHz) and ^{19}F NMR spectra were obtained using an 11.7 T Eclipse + (JEOL), with a broad band autotune 5 mm probe (JEOL). Residual protic solvent was used as an internal reference. Chemical shifts are reported in parts per million. Mass spectra were recorded on a Micromass AUTOSPEC-Q instrument (CI +, ammonia).

2, 3, 5, 6-*Tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate (**I**)*

Two hundred milligrams of 2-(2-nitroimidazol-1-yl) acetic acid (**II**)[6] and 290 mg 2,3,5,6-tetrafluorophenol were dissolved in 4 ml anhydrous THF. Three hundred and nine milligrams of DCC (1,3-dicyclohexylcarbodiimide) was dissolved in 7 ml anhydrous THF. The two solutions were mixed and left stirring overnight. The precipitate was filtered out. The solvent was evaporated under vacuum to give a tan solid. The crude product was purified immediately on a silica gel column, eluted with ethyl acetate/hexane (1:2) until TLC (ethyl acetate/hexane on silica TLC plate, visualized by UV) showed the absence of starting materials. The product was then eluted from the column using ethyl acetate. Evaporation of the solvent gave 210 mg (55%) of (I) as a tan solid.

^{1}H NMR data (CD_3CN): δ 7.4 (d, 1 H, imidazole proton), δ7.2 (d, 1 H, imidazole proton), δ 6.8 (m, 1 H, 4-phenyl proton), δ 5.5 (s, 2 H, CH_2).

^{19}F NMR data (CD_3CN, referenced to $CFCl_3$): δ -141 (m, 2F), δ -154 (m, 2F). Mass spec: Major peaks m/z 320 (I)H^+, m/z 337 (I)NH_4^+. Minor peak m/z 188 (II)H^+.

Conclusion

The synthesis of 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate by direct coupling of 2-(2-nitroimidazol-1-yl) acetic acid with 2,3,5,6-tetrafluorophenol, using the coupling agent, DCC, has been carried out in a 55% yield. This method is both faster and requires fewer steps (and reagents) than the method currently in use.

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