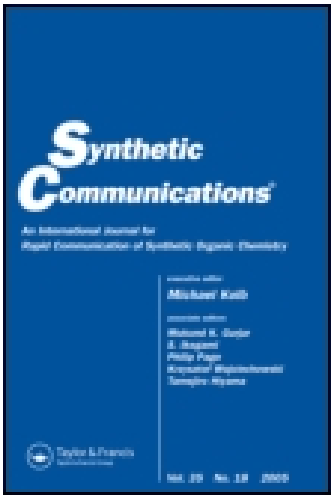


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient, Large-Scale Preparation of 2,4-Dichlorophenyl-4-bromomethyl-phenoxyacetate Suitable for Resin Anchorage of the First Fmoc Amino Acid

Loic René [a] & Bernard Badet [a]
[a] Institut de Chimie des Substances Naturelles, C.N.R.S. , 91198, Gif-sur-Yvette, Cedex, France
Published online: 04 Jan 2007.

To cite this article: Loic René & Bernard Badet (1994) A Convenient, Large-Scale Preparation of 2,4-Dichlorophenyl-4-bromomethyl-phenoxyacetate Suitable for Resin Anchorage of the First Fmoc Amino Acid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:4, 463-465, DOI: 10.1080/00397919408011495

To link to this article: http://dx.doi.org/10.1080/00397919408011495

SYNTHETIC COMMUNICATIONS, 24(4), 463-465 (1994)

A CONVENIENT, LARGE-SCALE PREPARATION OF 2,4-DICHLOROPHENYL-4-BROMOMETHYL-PHENOXYACETATE SUITABLE FOR RESIN ANCHORAGE OF THE FIRST FMOC AMINO ACID

Loïc René and Bernard Badet*

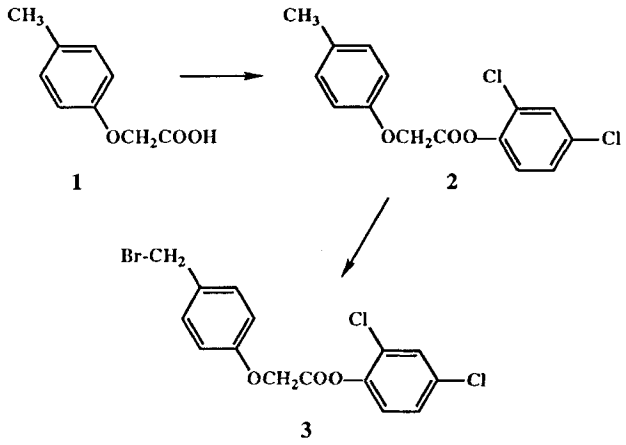
Institut de Chimie des Substances Naturelles, C.N.R.S.,
91198 Gif-sur-Yvette Cedex, France

ABSTRACT: 2,4-dichlorophenyl-4-bromomethyl-phenoxyacetate **3** was prepared by NBS treatement of 2,4-dichlorophenyl-4-methylphenoxyacetate **2**. This ester is a key intermediate in the preparation of 2,4-dichlorophenyl-N$^{\alpha}$-Fmoc-aminoacyl-4-oxymethylphenoxy-acetates suitable for anchorage of the first amino acid on amine-functionalized polymers.

Anchorage of the first N$^{\alpha}$-Fmoc-amino acid to solid supports as well as the corresponding nature of the linkage contribute to the yield and purity of the final peptide. Among the numerous methods which have been used to prepare the acid-labile 4-oxymethylphenoxyacetyl linkage[1-4] the esterification of hydroxyl-functionalized solid matrix support is probably the most popular. An alternative route involves direct acylation of support with 2,4-dichlorophenyl-N$^{\alpha}$-Fmoc-aminoacyl-4-oxymethyl-phenoxyacetates **4**[5]. The key step of this process is bromination of the poorly soluble 4-methylphenoxyacetic acid **1** which proceeds with only 36-55% yield. We found that the 2,4-dichlorophenyl ester **2** of this acid, easily prepared by esterification with 2,4 dichlorophenol using dicyclohexyl-

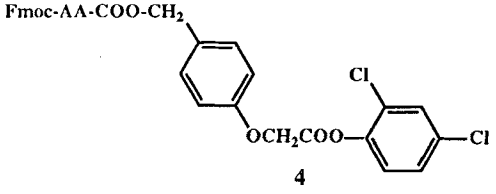
* To whom correspondence should be addressed

carbodiimide, afforded 2,4-dichlorophenyl-4-bromomethyl-phenoxy-acetate **3** in 80% yield upon treatment with NBS in chloroform (Scheme 1).



Scheme 1

As already described[5] 2,4-Dichlorophenyl-N$^{\alpha}$-Fmoc-aminoacyl-4-oxy-methyl-phenoxyacetates **4** (Scheme 2) prepared from bromo derivative **3** and N$^{\alpha}$-Fmoc-aminoacids readily react with polyamide-kieselguhr resin or other amino support and this coupling can be effectued "on line" in continuous-flow synthesis[6].



Scheme 2

Experimental Section

2,4-dichlorophenyl-4-methylphenoxyacetate (2): A solution of 4-methyl-phenoxyacetic acid **1** (99.6g, 0.6 mol), 2,4-dichlorophenol (108g, 0.66 mol) in tetrahydrofuran (1 L) was treated at 0°C with dicyclohexylcarbodiimide (124g, 0.6 mol). The mixture was stirred for two hours at room temperature, dicyclohexylurea was filtered off and tetrahydrofuran eliminated under vacuum. The resultant solid was recrystallized from hexan/ethyl acetate 60/40 to give white crystals (165g,

88%); mp, 114-115°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s,3H), 4.91 (s, 2H), 6.90-7.50 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.82, 64.69, 114.05, 123.72, 127.04, 127.39, 129.43, 129.58, 130.88, 131.73, 144.42, 154.91, 166.00; Mass spectrometry (chemical ionization, isobutane): 315 (M+H+4, 10), 313 (M+H+2, 64), 311 (M+H, 100).

2,4-dichlorophenyl-4-bromomethyl-phenoxyacetate (**3**): A mixture of 2,4-dichlorophenyl-4-methylphenoxyacetate **2** (155.6g, 0.5 mol), N-bromo succinimide (97.9g, 0.55 mol) and 2,2'-azobisisobutyronitrile (AIBN, 0.82g, 0.005 mol) in chloroform (1.5L) was heated under reflux for 6h. The cold solution was filtered, washed three times with 0.5M $NaHCO_3$ then with water. After elimination of chloroform under vacuum, the solid was recrystallized from hexan/ethyl acetate 85/15 to give white crystals (158g, 81%); mp, 115-116°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (s,2H), 4.89 (s, 2H), 6.85-7.40 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.01, 64.83, 114.84, 124.08, 127.49, 127.84, 130.02, 130.33, 131.34, 132.19, 144.77, 157.49, 165.95; Mass spectrometry (chemical ionization, isobutane): 393 (M+H+4, 45), 391 (M+H+2, 100), 389 (M+H, 100), 313 ((M+H+4) - HBr), 311 ((M+H+2) - HBr), 309 ((M+H) - HBr).

References and Notes

1. For a general survey on SPPS with Fmoc strategy see: Solid phase peptide synthesis a practical approach, Atherton, E.; Sheppard R.C.; Practical Approach Series, Series Editor: Rickwood, D.; Hames, B.D., IRL Press at Oxford University Press, Oxford, 1989.
2. Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.*, **1990**, *31*, 1701-1704.
3. Green, J.; Bradley, K. *Tetrahedron*, **1993**, *49*, 4141-4146.
4. Akaji, K.; Kuriyama, N.; Kimura, T.; Fujiwara, Y.; Kiso, Y. *Tetrahedron Lett.*, **1992**, *33*, 3177-3180.
5. Bernatowicz, M.S.; Kearney, T.; Neves, R.S.; Köster, H. *Tetrahedron Lett.*, **1989**, *30*, 4341-4344.
6. Synthesis was performed using a MilliGen 9050 PepSynthesizer™.

(Received in the UK 08 July 1993)