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9-Hydroxy-9-(4-carboxyphenyl)fluorene - A New Linker for Solid Phase Synthesis

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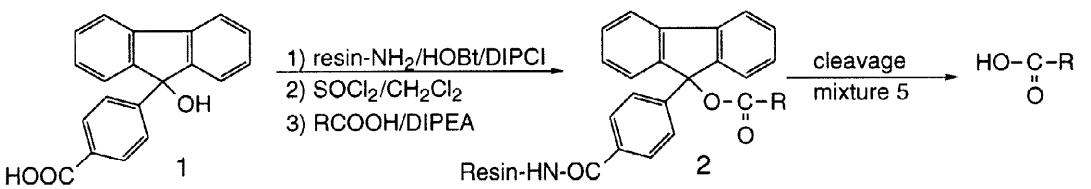
Abstract:

The convenient synthesis of 9-hydroxy-9-(4-carboxyphenyl)fluorene and its application as a new linker for solid phase synthesis is reported. The loading of the resin-bound linker with carboxylic acids as well as the cleavage conditions were investigated. The release of the carboxylic acids from this system by treatment with acids is hampered due to the electron-withdrawing effect of the carboxamide group in the para position of the phenyl ring of the resin-bound linker.

Keywords: Solid-phase synthesis; combinatorial chemistry; esterification; resins.

A strong demand exists for new linkers [1-3] suitable for use in solid phase chemistry. Especially those linkers are important which can be coupled to amino-functionalized polymers. Often acidic conditions cannot be used for solid phase chemistry because the bond between linker and desired molecule is cleaved. To combine acid stability of the ester bond to the linker with resin variability 9-hydroxy-9-(4-carboxyphenyl)fluorene **1** was synthesized (Scheme 1). The acid stability [4-6] of the ester linkage to the target molecule is compared to the system of Bleicher et al. [7,8] due to the electron-withdrawing effect of the carboxamide group of **2**.



Scheme 1. Use of 9-hydroxy-9-(4-carboxyphenyl)fluorene as linker for solid phase synthesis

Fluorenone was treated with 4-bromotoluene in a Grignard reaction to give 9-hydroxy-9-(4-methylphenyl)fluorene in 79% yield. This product was oxidized with $KMnO_4$/pyridine to

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give **1** in a yield of 75% after recrystallization from ethyl acetate: mp 185-186°C; FD-MS (field desorption): 302.2, $C_{20}H_{14}O_3$=302.3; ^{1}H NMR (in DMSO-D_6,ppm): 12.84 (COOH, s, 1H), 7.84, 7.83, 7.82, 7.81 (aromatic protons, 2d, 4H), 7.40, 7.38, 7.37, 7.36, 7.35, 7.34 (aromatic protons, 2t, 4H), 7.27, 7.26, 7.25, 7.24 (aromatic protons, 2d, 4H), 6.46 (OH, s, 1H); ^{13}C NMR (in DMSO-D_6, ppm): 168.0 (COOH), 151.8, 151.0, 140.1, 130.2, 130.1, 129.6, 129.1, 126.2, 125.5, 121.1 (aromatic carbons), 65.8 (C_9).

1 was coupled to aminomethylated polystyrene (test system) with hydroxybenzotriazole / diisopropylcarbodiimide followed by chlorination of the 9-position using thionyl chloride / dichloromethane (1:1) overnight. The resin-bound chlorinated linker was then treated with a fourfold excess of Fmoc-leucine in the presence of 5 eqs. of diisopropylethylamine for 2.5 hours to give **2** (Scheme 1). The coupling yield was 85% as determined by UV measurements [9].

To evaluate the cleavage kinetics the loaded resin was treated with several mixtures (Table 1) and the amount of liberated Fmoc-leucine measured with UV spectroscopy [9] after different time intervals.

Table 1
Cleavage of Fmoc-leucine under different conditions

Cleavage mixtures[1]	1	2	3	4	5
	27h	2h	1h	1h	1h
	no cleavage	39% cleavage	61% cleavage	69% cleavage	81% cleavage

[1]Mixture 1=96% trifluoroacetic acid (TFA), 2% H_2O, 2% $HSiEt_3$; mixture 2=92.5% TFA, 2.5% trifluoromethanesulfonic acid (TFMSA), 2.5% H_2O, 2.5% $HSiEt_3$; mixture 3=80% TFA, 10% MeOH, 10% TFMSA; mixture 4=76% TFA, 20% TFMSA, 2% H_2O, 2% $HSiEt_3$; mixture 5=66% TFA, 30% TFMSA, 2% H_2O, 2% $HSiEt_3$.

Table 1 shows that the ester bond between linker and Fmoc-amino acid remains stable towards TFA whereas the addition of TFMSA causes cleavage.

It was demonstrated that **1** can be synthesized easily and coupled to an amino group bearing polymer. The acidity of TFA is not sufficient to cleave the ester-bond to the 9-position of resin-bound linker, TFMSA must be added.

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